EUROPEAN CHEMICALS AGENCY

Helsinki, 27 April 2017

Addressee: [redacted]

Decision number: TPE-D-2114359618-36-01/F
Substance name: Reaction products of 1H-Imidazole-1-ethanol, 4,5-dihydro-, 2-(C11-C13 odd-numbered alkyl) derivs. and sodium hydroxide and chloroacetic acid
EC number: 938-645-3
CAS number: -
Registration number: [redacted]
Submission number: [redacted]
Submission date: 07.10.2016
Registered tonnage band: 100-1000T

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA examined your testing proposal(s) and decided as follows.

While your originally proposed test for a Sub-chronic toxicity study (90-day), oral route (EU B.26./OECD TG 408) and a Pre-natal developmental toxicity study (EU B.31./OECD TG 414) using the analogue substance Reaction products of 1H-Imidazole-1-ethanol, 4,5-dihydro-, 2-(C7-C17 odd-numbered, C17-unsatd. alkyl) derivs. and sodium hydroxide and chloroacetic acid (EC No 931-291-0) is rejected, you are requested to perform:

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

While your originally proposed test for **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)** using the analogue substance Acetic acid, chloro-, sodium salt, reaction products with 4,5-dihydro-2-undecyl-1H-imidazole-1-ethanol and sodium hydroxide (EC No 271-794-6) is rejected, you are requested to perform:

3. **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) using the registered substance.**

You are additionally requested to perform:

4. **Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: Daphnia sp. Acute Immobilisation Test, EU C.2/OECD TG 202) using the registered substance.**

5. **Growth inhibition study on aquatic algae and cyanobacteria (Annex VII, Section 9.1.2.; test method: Freshwater Alga and Cyanobacteria, Growth Inhibition Test, EU C.3 /OECD TG 201) using the registered substance.**

6. **Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: Fish, Acute Toxicity Test, EU C.1 /OECD TG 203) using the registered substance.**

7. **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) using the registered substance.**

In order to ensure use of the integrated testing strategy for the environmental requests, the acquatic short-term toxicity testing (no 4-6 above) are to be conducted first before long-term testing (no 4 and 8 above) is commenced, as further explained in Appendix 1, section 'Environmental testing'.

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 **6 May 2019**. 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

The decision of ECHA is based on the examination of the testing proposal(s) submitted by you.

0. Grouping of substances and read-across approach

a. Legal Background on ECHA's assessment of the grouping of substances and read-across hypothesis brought forward by the Registrant

ECHA based its decision on the examination of your testing proposals for the registered substance proposed to be performed with the analogue substances Reaction products of 1H-Imidazole-1-ethanol, 4,5-dihydro-, 2-(C7-C17 odd-numbered, C17-unsatd. alkyl) derivs. and sodium hydroxide and chloroacetic acid (thereafter Amphoacetates C8-C18 - EC No 931-291-0) and Acetic acid, chloro-, sodium salt, reaction products with 4,5-dihydro-2-undecyl-1H-imidazole-1-ethanol and sodium hydroxide (thereafter Amphoacetates C12 - EC No 271-794-6) and the submitted grouping and read-across justification.

The evaluation by ECHA of testing proposals submitted by registrants aims at ensuring that generation of information is tailored to real information needs. To this end, it is necessary to consider whether testing proposed by registrants are appropriate to fulfil the relevant information requirements and to guarantee the identification of health and environmental hazards of substances. In that respect, the REACH Regulation aims at promoting wherever possible the use of alternative means, where equivalent results to the prescribed test are provided on health and environmental hazards.

The first Recital and the first Article of the REACH Regulation establish the "*promotion of alternative methods for assessment of hazards of substances*" as an objective pursued by the Regulation. In accordance with that objective, ECHA considers whether a prediction of the relevant properties of the substance subject to this decision by using the results of the proposed test is sufficiently plausible based on the information currently available.

Article 13(1) of the REACH Regulation requires information on intrinsic properties of substances on human toxicity to be generated whenever possible by means other than vertebrate animal tests, including information from structurally related substances (grouping or read-across), "*provided that the conditions set out in Annex XI are met*".

Annex XI, 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.

b. Introduction of the grouping approach and read-across hypothesis proposed by the Registrant

According to the information provided in the category justification document attached to the technical dossier, you have developed a category of chemicals based on "*similarities in the general chemical process, functional groups and general composition*" and specified that "*the main variable resides in the alkyl chain distribution present in the raw materials*".

You indicated in the category justification document that the "*following substances are currently in the category*":

- Amphoacetates C8-C18, EC No 931-291-0
- Amphoacetates C12-14, EC No 938-645-3
- Amphoacetates C12, EC No 271-794-6

You concluded "*that based on the similar composition and structural similarity of the components present and their expected water solubility, partition coefficient, vapour pressure and surface activity, the substances of the chemical category will be distributed similarly in the environment and in the human body and may have similar (eco)toxicological properties*".

You proposed to conduct further testing with members of the category as detailed below:

- Sub-chronic toxicity study (90-day oral) according to the OECD TG 408 in rats proposed to be performed with the category member Amphoacetates C8-18. You justified the selection of this source substance "*because this substance is the mostly used substance of the category and because of its most complex composition. This substance contains also the smaller and higher alkyl chain derivatives and unsaturated C18 alkyl chain derivative, instead of only the C12 and C14 derivatives*".

- Pre-natal developmental toxicity study according to the OECD TG 414 in rats proposed to be performed with the category member Amphoacetates C8-18. You justified the selection of this source substance "*because of its most complex composition. This substance contains also the smaller and higher alkyl chain derivatives and unsaturated C18 alkyl chain derivative, instead of only the C12 and C14 derivatives. It is expected that this substance will show the highest absorption and (therefore) highest toxicity of the category*".

- Fish early-life stage (FELS) toxicity test according to the OECD TG 210 proposed to be performed with the category member Amphoacetates C12. You justified the selection of this species and this source substance since "*Based on the results obtained from the short-term toxicity studies, fish is considered substantially more sensitive than Daphnia and amphoacetates C12 seems to be the most hazardous to fish*".

You indicated in the category justification document that you consider it adequate to read-across the results from these proposed studies with source substances to the other members of the category (target substances) "*because the substances are considered similar based on the physico-chemistry data, their (eco)toxicological properties and their environmental fate and because the main components in the substances are similar (the C12 and C14 derivatives, characterised by an increase in C12 content)*".

c) Information submitted by the Registrant to support the grouping approach and read-across hypothesis

In order to support the grouping approach based on "*similarities in the general chemical process, functional groups and general composition*", you have provided information on each of these aspects in the category justification document.

Specifically, you have included a general overview of the chemistry of the manufacture of alkyl amphoacetates, outlining the main reactions involved in the synthesis of this type of substance.

You have also elaborated on the common structural features among the members of the category consisting in the presence of an amide bond, the presence of a hydroxyl group and an aminoglycinate function. You also presented theoretical structures of constituents of the category members and stressed that the "*precise structure (i.e. positioning of the acetate and hydroxyl groups) and respective percentages are variable and cannot be analytically determined due to the lack of a suitable analytical method for these complex UVCB substances*".

Information on the typical composition of each category member was presented with details of the alkyl chain distribution for each member of the category. You further identified differences in the composition of the category members and associated this variability with the use of starting materials containing a mixture of constituents with different alkyl chain lengths. You also reported that "*All substances in the category contain mono- and diacetate structures and contain a majority of the C12 and C14 derivatives. The ratio of mono and di-acetate constituents can be different due to the relative amount of chloroacetic acid used in the manufacturing process*".

In addition, information outlining similarities in physico-chemical properties of the category members and your assessment of the impact of these similarities on the distribution of the substances in the environmental and physiological compartments was reported.
You concluded on the basis of this information that "*the substances of the chemical category will be distributed similarly in the environment and in the human body and may have similar (eco)toxicological properties*".

In order to support the read-across approach within this category, you have elaborated on similarities in multiple physico-chemical properties among the members of the category such as water solubility, vapour pressure, density, flammability and pyrophoric and explosive properties. You also attributed differences in other properties such as melting point to the relative content of molecules with a similar alkyl chain length affecting their organisation when crystallising and melting. A data matrix presenting a range of physico-chemical properties for the three members of the category was included in the category justification document.

Similarly, you have presented and compared information on environmental fate and eco-toxicological properties of the category members in a data matrix. You concluded that all category members are considered to be readily biodegradable, are not expected to adhere to organic matter and would mainly reach the aquatic compartment. You further elaborated on the outcome of aquatic toxicity data available for the amphoacetates C8-18 and C12 and concluded that "*amphoacetates C8-C18 has a similar toxicity towards fish and Daphnia (L(E)C50's: 2.5 – 18.5 mg/L), while amphoacetates C12 is clearly more toxic towards fish than towards Daphnia (and more toxic towards fish than amphoacetates C8-C18)*". You considered that since "*amphoacetates C12-C14 has also mainly C12 and C14 mono- and diacetates similar to the tested substances, amphoacetates C12-C14 is considered to have a similar toxicity and is readacross to the lowest value in the category*".

You have reported your assessment of a set of available toxicological data for the category members and compiled this data in a matrix. Information on toxicokinetic properties, acute toxicity, skin and eye irritation, skin sensitisation, genotoxicity and repeated dose toxicity was evaluated. On that basis, you considered that "*the assumption that the properties of the members of the category are similar was also verified*".

d) ECHA analysis of the grouping approach in light of the requirements of Annex XI, 1.5

On the basis of the information provided in the category justification document ECHA understands that the grouping approach is based on similarities in the general chemical process, similarities in functional groups and similarities in the general composition of the members of the category.

The category justification document contains information on the alkyl chain distribution, established on the basis of the raw materials used to manufacture these substances, and high level information on the composition of these substances. You indicated that "*An important difference is the use of various types of raw materials, differing mainly by the linear alkyl chains present in the carboxylic acid starting material. UVCB-type substances derived from oleochemicals consist in mixtures of multiple chain lengths at varying amounts. The amount of each chain length depends on the source of fatty acids, which usually originates from natural fats and oils (containing for example the alkyl chain range from C8 to C18) but can also be from synthetic origin*". You also described in that document general structures of the main constituents, and indicate the presence of mono and diacetates in the composition of the difference substances. According to the information included in the category justification document, the "*ratio of mono and di-acetate constituents can be different due to the relative amount of chloroacetic acid used in the manufacturing process*".

The raw materials used and their ratio in the manufacturing process may lead to important variations in the composition of the substances, affecting both the distribution of the alkyl chain length and the ratio of mono- and diacetate for each alkyl derivative. The limited, generic information on the composition of the members of the category provided in the category justification document does not allow ECHA to verify the claimed compositional similarity. Specifically, no information on the typical concentration and on the concentration ranges discriminating the mono- and diacetates for each alkyl derivative included in the composition of the substances is provided. Therefore, ECHA considers that you have not sufficiently characterised the structural and compositional similarity and variability of the substances concerned by the category.

ECHA further points out that the category definition, as described in your category justification document, does not define the applicability domain of this category. You have described similarities in the chemistry and in the physico-chemical properties of the members of the category. You also identified factors causing some variability in the composition of the substances included in the category, such as the use of various types of raw material, differing mainly in the alkyl chain length, and the amount of chloroacetic acid used in the manufacturing process of the substances. Whilst this information presents similarities and possible differences among the three substances presented as members of the category, it does not constitute a set of inclusion and exclusion rules establishing the molecular structure that a substance must have to be part of the category and describing the accepted structural differenes within the category.

According to the ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6, such criteria should be described in order to identify the range of values within which reliable estimations can be made for the members of the category and to define the borders of the category. In the absence of a clear identification of the applicability domain of the category, ECHA considers that this grouping approach does not fulfil the requirement set in Annex XI, section 1.5 whereby "*Substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or category of substances*".

Consequently, for the reasons presented above, ECHA considers that the category approach, as currently documented in your dossier and applied to the proposed testing on sub-chronic toxicity (90-day), pre-natal developmental toxicity and long-term fish toxicity of these substances, does not fulfil the requirement defined in Annex XI, 1.5. Nevertheless, the determination that these substances cannot be considered as a category in accordance with Annex XI, 1.5 does not affect the possibility for you to invoke a read-across approach in order to predict human health effects and environmental effects of these substances individually on the basis of a one-to-one analogue approach. Irrespective of the unsuitability of the category approach, ECHA also analysed your proposal to predict properties of the registered substance from a test to be performed on the proposed source substance (one-to-one analogue approach).

e) ECHA analysis of the read-across hypothesis in light of the requirements of Annex XI, 1.5

Toxicological properties

You have proposed to perform testing for sub-chronic toxicity (90-day) and pre-natal developmental toxicity using the substance Amphoacetates C8-C18 (EC No 931-291-0) as source substance and proposed to read-across the results from these studies to the target substances Amphoacetates C12-14 and Amphoacetates C12.

According to the provisions of Annex XI, section 1.5 of the REACH Regulation, application of the group concept requires that physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach). ECHA understands from the information provided in the category justification document that your hypothesis according to which you consider that you can predict the properties of the substances within this read-across approach is based on your consideration that *"the substances are considered similar based on the physico-chemistry data, their (eco)toxicological properties and their environmental fate and because the main components in the substances are similar (the C12 and C14 derivatives, characterised by an increase in C12 content)"*.

ECHA observes that there is limited information supporting some elements of this read-across hypothesis in the registration dossier.

- Absence of a property-specific read-across justification

ECHA points out that you have not explained in a property-specific read-across justification on how and why the claimed structural similarity, and in this specific case also the claimed compositional similarity, among source and target substances constitute a basis to predict the properties sub-chronic toxicity (90-day) and pre-natal developmental toxicity.

- Characterisation of the composition of the substances

You refer in your read-across hypothesis to similarities in the main constituents of the substances, with a particular emphasis on the C12 and C14 derivatives. As outlined in section d) above, ECHA considers that the limited information on the chemical structures and the compositions of the source and target substances is not sufficient to verify that the main constituents of the substances included in this read-across approach are indeed similar.

- Assessment of the impact of the identified structural and compositional differences among the substances

You have identified qualitative and quantitative differences in the composition of source and target substances and associated them with the use of starting materials containing a mixture of constituents with different alkyl chain lengths. You indicated that "*Because most often from a natural origin, the C8-18 alkyl distribution is variable, and can only be given as a range of chain lengths, with the main constituents being C12 and C14. Fractionation can increase the content in specific chain lengths (for example, to > 90% C12-alkyl)*" and specified that "*In the three substances discussed in the present document, the alkyl chain distribution is centred on the C12 alkyl, i.e. it represents the majority of the alkyl chain present in the raw materials used, with a pattern of increasing C12-alkyl content*".

ECHA understands from this information that there are variations in the chain length distribution of the alkyl derivatives and/or the proportion of the different alkyl derivatives in the composition of the substances. You have selected the substance Amphoacetates C8-18 to perform the proposed studies for sub-chronic toxicity and pre-natal developmental toxicity and to read-across this data to Amphoacetates C12-14 and Amphoacetates C12. You indicated in the category justification document that this source substance had been selected for testing "*because of its most complex composition. This substance contains also the smaller and higher alkyl chain derivatives and unsaturated C18 alkyl chain derivative, instead of only the C12 and C14 derivatives. It is expected that this substance will show the highest absorption and (therefore) highest toxicity of the category*".

  - Differences in the distribution of alkyl derivatives

Based on the information provided in your category justification document, the substance Amphoacetates C8-18 has the widest alkyl chain distribution, ranging from C8 to C18 saturated and unsaturated derivatives, whereas the alkyl chain derivatives for the substances Amphoacetates C12-14 and Amphoacetates C12 are mainly in the range of C12 and C14. No unsaturated alkyl derivatives are reported in the composition of Amphoacetates C12-14 and Amphoacetates C12. It is not clear why "the most complex composition" qualifies this substance for the selection as source substance for target substances with less complex compositions.

ECHA observes that you have not elaborated on the potential impact of the presence of up to [redacted]% of unsaturated alkyl derivatives in the composition of the proposed source substance on the prediction of properties of Amphoacetates C12-14 and Amphoacetates C12. Similarly, ECHA observes that you have not provided any adequate explanation on the impact of the broader alkyl chain distribution in the proposed source substance on the prediction of the properties of Amphoacetates C12-14 and Amphoacetates C12. In this respect, ECHA further notes that whilst you indicated that among the substances considered in this read-across approach *"the alkyl chain distribution is centred on the C12 alkyl, i.e. it represents the majority of the alkyl chain present in the raw materials used, with a pattern of increasing C12-alkyl content",* the substance that you have selected as source substance has the lowest content in C12 alkyl derivatives. Based on the compositional information reported in the documentation of your approach, the C12 proportion of the alkyl chain distribution of Amphoacetates C8-18 may vary from [redacted]% to [redacted]%. This proportion is [redacted]% to [redacted]% for the Amphoacetates C12-14 and exceeds [redacted]% for the Amphoacetates C12. ECHA also highlights that you stated in your category justification document that the composition of Amphoacetates C12-14 "*is more closely related to the composition of the substance amphoacetates C12; as it contains [redacted]% of the C12 alkyl derivatives and lacks the smaller and higher alkyl chain derivatives and unsaturated C18 alkyl chain derivatives*". Taken together this information suggests that Amphoacetates C8-18 may not represent the closest composition to Amphoacetate C12-14. In the absence of further justification addressing the differences in the composition among these substances, the adequacy of Amphoacetates C8-18 as a source substance to predict properties of Amphoacetates with a significantly higher content in C12 alkyl derivatives such as Amphoacetates C12-14 and Amphoacetates C12 is questioned.

- Toxicokinetic properties

Furthermore you have not provided a scientific argument to support your assumption that the Amphoacetate C8-C18 will show the highest absorption. ECHA assumes that you consider that shorter chain lengths alkyl derivatives in the composition might have a higher absorption. In this case, ECHA points out that the assessment of the impact of the common and varying structural features (e.g. amide bonds, mono-acetates, diacetates, hydroxyl groups) on the absorption of the constituents has not been included in your documentation. ECHA also notes that in your assessment of the toxicological properties of the substances reported in section 5 of your category justification document you considered that "*Oral, dermal and inhalation absorption rates of 100%, 10% and 100% were estimated, respectively*" for Amphoacetates C8-18 and that "

As amphoacetates C12-C14 and amphoacetates C12 contain surfactant constituents structurally similar to the assessed substance and all have similar physico-chemical properties,amphoacetates C12-C14 and amphoacetates C12 are considered to have similar oral, dermal and inhalation absorption rates of 100%, 10% and 100%, respectively". This conclusion appears to be inconsistent with your argument for selection of Amphoacetates C8-18 as source substance for further testing based on a "*highest absorption*". The source and target substances in this read-across approach are UVCBs. The large number of constituents associated with these type of substances and the structural differences among these constituents limit the relevance of a conclusion on the overall absorption of the substance without discriminating the relative absorption of the different constituents in the context of a read-across approach. ECHA furthermore understands from the information provided that you therefore expect a relationship between increasing absorption and toxicity of the constituents. This assumption is not substantiated with evidence supporting that such a relationship exists for the constituents of the source substance.

On the basis of the compositional information currently reported, it appears that the range of constituents to which the test organism is exposed to after administration of Amphoacetates C8-18 is likely to be different from that after administration of Amphoacetates C12-14 or Amphoacetates C12. ECHA notes that you have not established that the strutural differences such as the alkyl chain length, mono or diacetate structures do not lead to differences in the systemic absorption of these constituents. ECHA further highlights that no or very limited information on the metabolism, distribution, and excretion of the different constituents and their breakdown products has been reported in your category justification document. In the absence of information on these aspects, it remains unclear which constituents of these substances are systemically available. Consequently, a plausible mechanistic explanation cannot be presented on why and how test results from the source substance can be used to predict systemic properties for the target substances. ECHA considers that you have not established that the properties of these substances relating to systemic toxicity are likely to be similar or follow a regular pattern. Therefore, ECHA considers that you have not provided an adequate scientific basis according to which the properties of Amphoacetates C12-14 and Amphoacetates C12 for the endpoints sub-chronic toxicity and pre-natal developmental toxicity may be predicted from data generated using Amphoacetates C8-18.

- Variations in the ratio of mono- vs diacetates

You have indicated in your category justification document that "*All substances in the category contain mono- and diacetate structures and contain a majority of the C12 and C14 derivatives. The ratio of mono and di-acetate constituents can be different due to the relative amount of chloroacetic acid used in the manufacturing process*" and provided generic theoretical structures of these mono and diacetates. In your assessment of the variability and differences among the substances, you considered that "*The ratio of the (potential) structures contained in the surfactant part of the substance is not expected to play a significant role with regard to the (eco)toxicological properties of the substances, because the structures all have the same functional groups, i.e. one or two aminoglycinate (-NH-CH2-COONa) functions (i.e. terminal acetate) and hydroxyl, linked to a fatty chain by an amide bond*".

As outlined in section d) above, no information on the typical concentration and on the concentration ranges discriminating the mono and diacetates for each alkyl derivative included in the composition of the substances is provided. ECHA stresses that the presence of qualitatively similar functional groups such as hydroxyl groups, acetates or alkyl chains in the structure of the constitutents of the source and target substances does not in itself establish that these constituents have similar toxicological properties. On the basis of the information provided ECHA considers that you have not provided scientific information to establish that the possible variations in the number and position of the different functional groups and variations in the alkyl chain length do not impact the toxicological properties of the constituents, and in turn the toxicological properties of the source and target substances.

Furthermore, according the provisions of Annex XI, section 1.5 of the REACH Regulation the toxicological properties of substances included in read-across approaches should be "*likely to be similar or follow a regular pattern as a result of structural similarity*". Based on the information provided in your registration dossier, ECHA considers that there are indications that the toxicological properties of the substances included in this read-across approach differ, as outlined below.

ECHA understands that one of the elements contributing to your consideration that the substances included in this read-across approach are considered similar is their toxicological profile. Whilst the available data on the substances included in this read-across approach and reported in the data matrix provided in the category justification document may suggest similarities in the properties of these substances for properties such as acute toxicity, skin irritation and skin sensitisation, ECHA observes differences in the properties for the endpoints eye irritation, i.e. different classification categories for the substances, and in vitro cytogenicity between the Amphoacetates C8-18 and Amphoacetates C12. Such differences may be indicative of different reactivity in biological systems.

In addition, ECHA stresses that:

- the data set on the substance subject to this decision, i.e. Amphoacetates C12-14, is limited to oral and dermal acute toxicity data;
- only one data point addressing the property repeated-dose toxicity is available: a 28-day repeated-dose toxicity study performed with Amphoacetates C8-18;
- no information related to the property pre-natal developmental toxicity is available for any of the substances included in this read-across.

Therefore , ECHA considers that the information currently available on the toxicological properties of these substances does not constitute evidence supporting a claim of similarity of these substances. In addition, ECHA is of the opinion that it cannot be established from this data set that the properties of substances can be predicted from other substances in this read-across approach for the endpoints repeated-dose toxicity and pre-natal developmental toxicity.

Overall, for the reasons presented above and on the basis of the information provided in your registration dossier, ECHA considers that you have not provided adequate and reliable information to demonstrate that the proposed read-across approach complies with the criteria of Annex XI, Section 1.5. and is plausible for the endpoint(s) in consideration. Consequently the testing proposed on the read-across substance(s) is not appropriate to fulfil the information requirement(s) of the substance subject to the present decision.

Ecotoxicological properties

You have proposed to perform testing on a long-term toxicity to fish by using the source substance Amphoacetates C12 (EC No 271-794-6) and proposed to read-across the results of this study to the target substances. In addition, in your dossier for the registered substance all the aquatic toxicity studies are read-across from the other members of your category. You have used studies with Amphoacetates C8-C18 for fulfilling the information requirement of short-term toxicity to aquatic invertebrates. For toxicity to long-term aquatic invertebrates you have provided the following adaptation statement: "*This substance (amphoacetates C12-C14) is a member of the amphoacetate category. A long-term toxicity study with fish (OECD 210) will be performed with another member of the chemical category (amphoacetates C12) and this REACH Annex IX study will be read-across to this substance. Pending the outcome of this study, a long-term toxicity study with Daphnids with any member of the chemical category is waived as Daphnids are not the most sensitive species. The substance amphoacetates C12 is more than a factor of 50 more sensitive to fish than to Daphnids: 96h-LC50 (zebrafish): 1.6 mg/L vs. 48h-EC50: 89 mg/L.*" For short-term toxicity to fish and for growth inhibition study on aquatic plants (algae preferred) you have used studies with Amphoacetate C12.

ECHA understands from the information provided in the category justification document that your read-across hypothesis is based on your consideration that *"the substances are considered similar based on the physico-chemistry data, their (eco)toxicological properties and their environmental fate and because the main components in the substances are similar (the C12 and C14 derivatives, characterised by an increase in C12 content)"*.

Furthermore ECHA understands that the reasoning for your testing proposal using the source substance Amphoacetates C12 as test material is as follows: *"Due to their wide dispersive uses and their EU volumes, information about the long-term aquatic toxicity of the members of the category is considered to be essential. Based on the results obtained from the short-term toxicity studies, fish is considered substantially more sensitive than Daphnia and amphoacetates C12 seems to be the most hazardous to fish.*

The substance amphoacetates C12 is more than a factor of 50 more sensitive to fish than to Daphnids: 96h-LC50 (zebrafish): 1.6 mg/L vs. 48h-EC50: 89 mg/L. This study is proposed as it is considered as the most sensitive of the fish tests (in accordance with the ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b: Endpoint specific guidance, May 2008)."

ECHA observes that there is limited information supporting some elements of this read-across hypothesis in the registration dossier. In addition to issues that were already described under section d) above, ECHA observes that there are also limited information supporting some elements of the ecotoxicological read-across hypothesis in the registration dossier.

- Absence of a property-specific justification

ECHA points out that you have not explained in a property-specific justification why and how the claimed structural similarity, and in this specific case also the claimed compositional similarity, among source and target substances can be used to predict the aquatic toxicity properties. For example, you have not explained why you use source studies from Amphoacetates C8-C18 (EC No 931-291-0) to fulfil the information requirement for short-term toxicity to aquatic invertebrates for the Amphoacetates C12-C14 (EC 938-645-3) and in the same dossier submission you consider that there is no need to perform the test for long-term toxicity to aquatic invertebrates, because *"The substance amphoacetates C12 is more than a factor of 50 more sensitive to fish than to Daphnids: 96h-LC50 (zebrafish): 1.6 mg/L vs. 48h-EC50: 89 mg/L"*. Without property specific rationale and justification for example based on common mechanisms of action and similarities in chemical (or biochemical) reactivity it not possible for ECHA to understand and verify this read-across approach proposed in your dossier.

According to the general rules for adaptation of the standard testing regime set out in Annexes VII to X, and regarding specifically Annex XI, 1.5, in all cases, the results should be adequate for the purpose of classification and labelling and/or risk assessment. ECHA considers that in the grouping and read-across context this means that the predicted properties shall not underestimate the hazards, and the adequate and reliable documentation of the applied methods and approach proposed needs to be provided to allow ECHA to verify and accept the proposed adaptation according to Annex XI, 1.5.

- Supporting information for read-across in environmental endpoints

ECHA considers that it is important to provide supporting information to strengthen the rationale for the read-across. As part of your category justification, you have provided a data matrix containing physico-chemical properties for the category members. Also you have also provided a data matrix representing environmental fate and toxicity studies for the Amphoacetates category. ECHA notices that as all the substances in the category are UVCB and surfactants, the lack of detailed information on the test materials and sample preparation makes it difficult to compare the results reported in these two tables. Regarding the physco-chemical properties as a supporting information for read-across and grouping ECHA would expect, given the compositional variations, to see ranges of values and explanations for the variation between the results and if this would give rise to different aquatic toxicity effects. Alternatively, whether the information shows similarity of action or reaction can be assumed regardless of the variation observed. Furthermore, ECHA notes that there are no studies available for aquatic toxicity, biodegaradation and activated sludge respiration inhibition studies with the registered substance Amphoacetates C12-C14.

As all the substances in the category are surface active, it is known that they can form dispersions or emulsions in which the bioavailability is difficult to ascertain, even with careful solution preparation. Moreover, the micelle formation can result in an overestimation of the bioavailable fraction even when a solution seems to be formed. This may present significant problems of interpretation.

It is recommended in the ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b: Endpoint specific guidance, Version 3.0, February 2016, that *"Toxic effect concentrations for dispersions and emulsions should be compared with the dispersibility limit (i.e., the limit at which phase separation takes place) or the critical micelle concentration (CMC) for a substance in water rather than with its water solubility limit. The bioavailable concentration does not change above the CMC, even at higher dosing levels. The highest test concentration should either be 1000 mg active ingredient/litre or the dispersibility limit/CMC, whichever is lower."*

However, ECHA notes that you have not discussed the surface activity as a potential challenge in interpretation of the results obtained from the aquatic toxicity studies or for the selection of the test material for your testing proposal in your category justification document or in the technical dossier.

- Source data quality

The two key studies for your testing proposal justification establishing the sensitivity between Daphnia and fish are on short-term toxicity to fish and aquatic invertebrates tested with source substance Amphoacetates C12. Yet, you have not provided the robust study summary for the short-term toxicity to aquatic invertebrates in your registration dossier, instead the results of the that study are referred to as follows: *"The substance amphoacetates C12 is more than a factor of 50 more sensitive to fish than to Daphnids: 96h-LC50 (zebrafish): 1.6 mg/L vs. 48h-EC50: 89 mg/L."*.

Furthermore, based on your robust study summary the short-term fish toxicity test was conducted according to test method ISO 7346-1 (Determination of the Acute Lethal Toxicity of Substances to a Freshwater Fish [Brachydanio rerio Hamilton-Buchanan (Teleostei, Cyprinidae)] - Part 2: Semi-static method) and GLP ([redacted]., 1993). You have reported that the test material form was an aqueous solution and that the confidential details of the test material are as follows: "*Name of the test material (as cited in study report)* "[redacted] *composition of test material reported as percentage of components: solid content ± 35% (33-36%), water content ± 65% (64-67%), surfactant content 18-23%, NaCl content: 6.5-8.5%, Sodium glycolate 4-9%*". Results for semi-static freshwater 96 h LC50 for fish with Amphoacaetates C12 is 1.6 mg/L, concentration expressed as solid content (nominal), results are based on mortality (lower and upper confidence limit not reported).

ECHA considers that the key study on short-term fish toxicity that you have provided cannot be regarded as adequate, reliable and valid source study to support your read-across approach for the following reasons:

The registered substance is surface active and UVCB. Yet, in the confidential details on the test material the you state that: "*the CAS number in the report is correct; the chemical description and purity information is incorrect (separately confirmed)*". Therefore, ECHA cannot verify that the test material which has been tested is actually consistent and representative of the substance being registered. Furthermore, there is lack of information on the statistical methods used in the calculations and also the only details given of the test solutions are the following:"*1 g of the testmaterial (aqueous solution) was dissolved in 1 L synthetic water. From this stock solution, the test solutions were prepared.*"

Furthermore, due to the absence of measured concentrations of the test material during the test, especially when the registered material is known to be surface active (see the subsection above), it is impossible to verify the reliability of the test results reported. In addition, the fish length and weight are not reported which makes it difficult to ascertain the equal sensitivities of the test organisms.

Also, when reporting the results of the analytical monitoring you made the following statement which makes your statement on maintenance of test concentrations above [redacted]% of the nominal invalid:" *The irrelevance of the DOC measurements is supported by the fact that the measurements at t=0 are higher than the nominal DOC values as well as by the fact that DOC values increase during the test (which is easily understandable as biological activity probably causes this increase).*"

Overall, ECHA considers that based on all the deficiencies reported above, the validity criteria of short-term fish toxicity testing cannot be considered fulfilled and the reporting is not adequate, so the test results cannot be considered to be reliable. Consequently, the information provided for the registered substance in the technical dossier does not meet the information requirement. Since the information from the short term toxicity studies on fish and aquatic invertebrates is inadequate then it cannot be used to support the proposed testing and the adaptation strategy for short- and long-term aquatic toxicity of the registered substance fails.

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Consideration of your comments and updated dossier

You have submitted a dossier update on 07 October 2016 (submission number [redacted]). This dossier update includes a document entitled "[redacted] dated on 06 October 2016 in IUCLID section 13. This document contains your views on the points raised by ECHA in the draft decision and describes a proposed step-wise approach to fulfil the data gaps in the dossiers of the members of this category.
Specifically, you indicate that:

- You acknowledge the points raised by ECHA on the limited information on the composition of the members of the category and express their intention to "*undertake more efforts to more adequately specify the substance's composition in order to support the verification of substance similarity. Also, in a tiered approach, new techniques are planned to be explored, e.g. HPLC-NMR, to address the mono-/diacetate ratio questions*".

- You also agree that the borders of the category were not specifically defined. You report that analytical data will be generated to refine the category definition and that based on this new data a decision on whether to pursue in a category approach or to switch to analogue approaches will be made.

- the read-across approach will be revised on the basis of new analytical data. You specify that the read-across approach will be reconsidered based on the RAAF and inform that a tiered testing approach to address toxicological endpoints – specifically sub-chronic repeated dose toxicity and reproductive/developmental toxicity – is being developed and that possibilities to use data on metabolism and toxicokinetics of the analogues to justify the read-across are being explored .

  In the description of their "Step-wise approach to fill the data gaps in the dossiers", you outline the steps already taken and planned to be started:
  - Additional information on the test material used in the available studies has been included in the updated dossiers, with an emphasis on alkyl chain length distribution and/or mono/diacetate ratio.
  - Improve the analytical data sets of analogues, with a particular effort to determine the monoacetate/diacetate ratio.
  - Reconsider the read-across approach and fill the data gaps on toxicological endpoints through *A step-wise approach [...], which will include additional test work and potentially data on metabolism and toxicokinetics of the category members to strengthen the read-across hypothesis*

You consider that this strategy is scientifically valid and respects the principles of animal use reduction and welfare. You also outline that the timeline envisioned by ECHA to have all the information generated within 30 months is very ambitious.

ECHA acknowledges and welcomes your intentions to provide further information on the composition of the members of the category. ECHA observes that the information provided in the upated dossier, i.e. your intentions to generate new analytical data and to revise your read-across approach on that basis and to develop a tiered approach including additional test work and potentially data on metabolism and toxicokinetics information, is informative about your general intentions and plans.

However the information provided in your comments and in the updated dossier does not include new scientific arguments and evidence for ECHA to assess..

You indicated in your updated dossierthat the revision of your read-across approach will be based on ECHA's read-across assessment framework (RAAF). ECHA draws your attention to the fact that the RAAF has been developed for assessing read-across approaches for predicting toxicological properties based on mono-constituent substances. The application of grouping and read-across approaches to UVCB substances, such as the substance subject tot his decision, requires additional scientific considerations. ECHA will shortly publish on its website a document presenting aspects to be taken into account when evaluating such grouping and read-across approaches. ECHA understands from the information provided in the dossier update that the scientific data constituting the basis for the revised adaptation is not yet available. The information provided in the dossier update does not allow ECHA to conclude on whether the step-wise approach described in very generic terms in your dossier update will be acceptable or plausible to meet the information requirements under consideration. Therefore, in the absence of new scientific information, ECHA considers that based on the information currently provided, there is no basis on which to revise the ECHA's conclusions from the scientific assessment of your adaptation, and and proposed testing of the source substance cannot be considered plausible for the endpoint(s) in consideration of the registered substance.

Furthermore, ECHA notes that you have commented on the the timeline given in this decision, but you have not demonstrated its inappropriateness or required (with any justification) an extension. ECHA considers that a deadline of 24 months is a reasonable time period for providing the required information in this decision in the form of an updated registration from the date of the adoption of the decision.

e) Conclusion

Furthermore, for the reasons presented above and on the basis of the information provided in your registration dossier, ECHA considers that your read-across hypothesis based upon similarities in physico-chemical and (eco)toxicological properties is not supported by reliable and comparable evidence and therefore ECHA is not in the position to verify and accept the adaptation proposed. In addition, as explained above you have not provided a property-specific justification for why aquatic toxicity may be predicted for Amphoacetates C12-C14 by using data generated with Amphoacetates C12 and/or Amphoacetates C8-C18.
Based on the above considerations ECHA concludes that you have not provided adequate and reliable information to demostrate that the proposed read-across is plausible for the endpoint(s) in consideration.

ECHA therefore concludes that the criteria of Annex XI, Section 1.5. are not met, and consequently the testing proposed on the source substance is not appropriate to fulfil the information requirement(s) of the substance subject to the present decision.

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

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

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. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a sub-chronic toxicity study (90 day) in rats by the oral route according to EU B.26./OECD TG 408 with the analogue substance Amphoacetates C8-C18 (EC No 931-291-0).
ECHA has evaluated your proposal to perform the test with the analogue substance Amphoacetates C8-C18 (EC No 931-291-0). As explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

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 4.1, October 2015) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the registered substance is a solid marketed or used in aqueous solution and there are no indications for significant inhalation exposure of humans (e.g., spray application). 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.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the additional study with the registered substance subject to the present decision: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26./OECD TG 408) while your originally proposed test for a Sub-chronic toxicity study (90-day) with the analogue substance Amphoacetates C8-C18 (EC No 931-291-0) is rejected according to Article 40(3)(d) of the REACH Regulation.

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

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

A pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a pre-natal developmental toxicity study in rats according to EU B.31./OECD TG 414 by the oral route with the analogue substance Amphoacetates C8-C18 (EC No 931-291-0).

ECHA has evaluated your proposal to perform the test with the analogue substance Amphoacetates C8-C18 (EC No 931-291-0). As explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

ECHA considers that the proposed test method is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

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 the rat or rabbit 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 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a a solid marketed or used in aqueous solution, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the additional study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a first species (rats or rabbits), oral route (test method: EU B.31./OECD TG 414) while your originally proposed test for a Pre-natal developmental toxicity study with the analogue substance Amphoacetates C8-C18 (EC No 931-291-0) is rejected according to Article 40(3)(d) of the REACH Regulation.

Notes for your consideration

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015), Chapter R.7a, section R.7.6.2.3.2.

Environmental testing:

In order to ensure use of the integrated testing strategy, the aquatic short-term toxicity testing on algae, *Daphnia* and fish are to be conducted first to determine the most sensitive species for the aquatic long term toxicity testing.

If, based on the results, either fish or aquatic invertebrates are shown to be substantially more sensitive than the respective other species, according to ECHA Guidance on information requirements and chemical safety assessment (version 3.0, February 2016), Chapter R7b (Section R.7.8.5 including Figure R.7.8-4), a long-term study on the more sensitive species is required, i.e. either on invertebrates or fish. On the contrary, 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 a case, according to the integrated testing strategy, the invertebrate study (*Daphnia* preferred) is to be conducted first. If, based on the results of the long-term invertebrate 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, then also long-term fish testing may need to be conducted.

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

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

"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. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for testing the analogue substance Amphoacetates C12 (EC No 271-794-6) for long-term toxicity testing on fish according to Fish, early-life stage toxicity test, OECD TG 210 with the following justification: "*This substance (Amphoacetates C12-14) is a member of the amphoacetates category. A long-term toxicity to fish study (OECD 210) will be performed with another member of the chemical category (amphoacetates C12, EC 271-794-6) and this REACH Annex IX study will be read-across to this substance*.".

ECHA has evaluated your proposal to perform the test with the analogue substance Amphoacetates C12 (EC No 271-794-6). As explained above in Appendix 1, section 0 of this decision, your adaptation provided in your comments on the draft decision and updated technical dossier of the information requirement is rejected.
ECHA notes that you have not submitted a testing proposal on a "Long-term toxicity testing on invertebrates", which is a standard information requirement as laid down in Annex IX, Section 9.1.5. of the REACH Regulation. Furthermore, there were no indications in the dossier from the short-term toxicity studies on aquatic species that fish would be substantially more sensitive than aquatic invertebrates or algae.

In your dossier you have no aquatic toxicity data available with the registered substance. Instead, you have sought the adaptation under Annex XI, 1.5 and provided studies with analogue substances to fullfil the standard information requirements for the short-term aquatic toxicity studies and the growth inhibition study on aquatic algae and cyanobacteria within the category of Alcylamphoacetates. In addition, you have adapted the standard information requirements for the long-term toxicity testing on invertebrates based on short-term aquatic toxicity studies on the analogue substance Alcylamphoacetate C12. As explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected. Consequently, there are data gaps in your dossier on aquatic toxicity and the sensitivity between the aquatic species cannot be established. The additional request to conduct the long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.) and the additional short-term aquatic toxicity studies will be addressed in the Sections 4 to 7 of this decision (below).

ECHA considers that the proposed test method is appropriate to fulfil the information requirement of Annex IX, Section 9.1.6 of the REACH regulation.

Therefore, pursuant to Article 40(3)(c)of the REACH Regulation, you are requested to carry out the proposed test using the registered substance subject to the present decision: Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.; test method: Fish, early-life stage toxicity test, OECD TG 210) while your originally proposed test for long-term toxicity on fish according with the analogue substance Amphoacetates C12 (EC No 271-794-6) is rejected according to Article 40(3)(d) of the REACH Regulation.

Notes for your consideration related to Appendix 1, sections 3-7

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 3.0, February 2016), 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.

Due to the UVCB and surface activity properties of the registered substance you should consult OECD Guidance document on Aquatic Toxicity Testing on Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA Guidance on information requirements and chemical safety assessment (version 3.0, February 2016), Chapter R7b, table R. 7.8-3 summarising aquatic toxicity testing on difficult substances for choosing the design of the requested long-term ecotoxicity tests and for calculation and expression of the result of this test.

4. to 7. Additional aquatic toxicity tests

4. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.),

5. Growth inhibition study on aquatic algae and cyanobacteria (Annex VII, Section 9.1.2.),

6. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.),

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

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

(i) Information provided by you on short term-toxicity test on aquatic invertebrates, short-term toxicity to fish, growth inhibition study on aquatic algae and cyanobacteria and long-term toxicity test on aquatic invertebrates.

For the standard information requirement of short-term toxicity on aquatic invertebrates, you have provided four key studies and two supporting studies with an analogue test material amphoacetate C8-C18 (EC No 931-291-0):

1) key study according to OECD TG 202, GLP, [redacted] (1992), with analogue test material name Ampholak XCO-30/Rewoteric AM2CNM (EC No 931-291-0; test material form aqueous solution; Lot/Batch No.: 1/86; composition of test material, percentage of components reported: surfactant concentration: 33.7%, separately reported: solid content: 39.5%, water content: 60.5%, NaCl content: 8.5%). Results: 48h EC50 2.5 mg/L concentration expressed as solid content (nominal) based on mobility (range: 2.1-3 mg/L);

2) key study according to EU Method C.2, GLP, [redacted] (1994), with analogue test material name Miranol C2M Conc NP (EC No 931-291-0, test material form aqueous solution; Batch/Lot number: LP943; composition of test material reported, percentage of components: solid content: surfactant content 39.3%, solid content 50.5%, water content: 49.5%, NaCl content: 11.2%). Results: 48 h EC50 12.6 mg/L concentration expressed as solid content (nominal) based on mobility (range: 8.1-16.7 mg/L);

3) key study according to OECD TG 202, GLP, [redacted] (1996), with analogue test material name Empigen CDR 60 (EC No 931-291-0, test material form aqueous solution; Batch/Lot number: E/2051; composition of test material reported, percentage of components: surfactant content: 32.9%, separately reported: solid content: 42%, water content: 58%, NaCl content: 9%). Results: 48 h EC50 18.5 mg/L concentration expressed as solid content (nominal) based on mobility (range: 16-21 mg/L);

4) key study according to OECD 202, GLP, [redacted] (2001), with analogue test material name Dehyton MC (EC No 931-291-0, test material form aqueous solution; Batch/Lot number: E/2051; composition of test material reported, percentage of components: surfactant content: 32%, separately reported: solid content: 39%, water content: 61%, NaCl content: 7%). Results: 48 h EC50 17.9 mg/L concentration expressed as solid content (nominal) based on mobility (no range reported);

5) supporting study according to OECD 202, non GLP, [redacted] (2010a), with analogue test material name Euroglyc MD (EC No 931-291-0, test material form aqueous solution; no Batch or Lot number reported; composition of test material reported, percentage of components: surfactant content: 38%, solid content: 50%, water content: 50%, NaCl content: 12%). Results: 48 h EC50 8.2 mg/L concentration expressed as solid content (nominal) based on mobility (range: 4.4-16.2 mg/L);

6) supporting study according to OECD 202, non GLP, [redacted] (2010b), with analogue test material name Euroglyc AMS (EC 931-291-0, test material form aqueous solution; no Batch or Lot number reported; composition of test material reported, percentage of components: surfactant content: 32.5%, solid content: 40%, water content: 60%, NaCl content: 7.5%). Results: 48 h EC50 6 mg/L concentration expressed as solid content (nominal) based on mobility (range: 3.1-12.3 mg/L).

For the standard information requirement of short-term toxicity to fish, you have submitted the following key study with analogue test material Amphoacaetate C12 (EC 271-794-6):

1) key study, according to ISO 7346-1 (Determination of the Acute Lethal Toxicity of Substances to a Freshwater Fish [Brachydanio rerio Hamilton-Buchanan (Teleostei, Cyprinidae)] - Part 2: Semi-static method) and GLP, [redacted] (1993), with analogue test material name E Dehyton W (EC 271-794-6, test material form aqueous solution; Batch/Lot No. 66283 / 51 Z 1600012000; composition of test material reported, percentage of components: solid content ± 35% (33-36%), water content 65% (64-67%), surfactant content 18-23%, NaCl content: 6.5-8.5%, Sodium glycolate 4-9%). Other information related to testing material composition: the CAS number in the report is correct; the chemical description and purity information is incorrect (separately confirmed)). Results: semi-static, freshwater 96 h LC50 1.6 mg/L concentration expressed as solid content (nominal) based on mortality (range not given).

For the standard information requirement toxicity to aquatic algae and cyanobacteria you have provided the following one key study with analogue test material Amphoacaetate C12 (EC 271-794-6):

1) key study, according to 201, non GLP, [redacted] (2008), with analogue test material name Miranol Ultra L-32 (EC 271-794-6, test material form aqueous solution; Lot/Batch No.: W17D081651; composition of test material, percentage of components, solid content: 38%, water content: 62%, separately reported: NaCl content: 7.6% (max.), surfactant content: 30-32%). Result: 72h EC50 14.8 mg/L concentration expressed as solid content (nominal) based on growth rate (range not given).

For the information requirement of long-term toxicity to aquatic invertebrates you have given the following statement: "*This substance (amphoacetates C12-C14) is a member of the amphoacetate category. A long-term toxicity study with fish (OECD 210) will be performed with another member of the chemical category (amphoacetates C12) and this REACH Annex IX study will be read-across to this substance. Pending the outcome of this study, a long-term toxicity study with Daphnids with any member of the chemical category is waived as Daphnids are not the most sensitive species. The substance amphoacetates C12 is more than a factor of 50 more sensitive to fish than to Daphnids: 96h-LC50 (zebrafish): 1.6 mg/L vs. 48h-EC50: 89 mg/L.*"

(ii) Assessment of the aquatic toxicity studies

You have sought to adapt the above listed information requirements (see sections 4 to 7 of the decision) by submitting test results of two analogue UVCB test materials: amphoacteates C12 (EC No 271-794-6) and amphoacetates C8-C18 (EC No 931-921-0). All of the above referred studies you have provided show the same deficiencies; in particular, a lack of sufficient information on the UVCB test material composition e.g. chemical identity of its constituents, their quantitative occurrence and relevant properties of the constituents. Lack of clarity of the tested materials and lack of adequate and reliable documentation on how these analogue test materials relate to the registered (target) substance, combined with source data quality and validity issues (as also explained in Section 0. of this decision) makes it impossible to ECHA to verify and consequently accept the adaptation as proposed.

As the category and read-across proposed in your dossier does not meet the general rules for adaptation under Annex XI section 1.5 (as explained in the Section 0. of this decision), there is a information gap in you dossier in all the aquatic toxicity studies addressed in sections 3-7 of this decision.

In the absence of reliable information on toxicity to algae, Daphnia and fish, it cannot be concluded if fish or invertebrates or algae/aquatic plants are shown to be substantially more sensitive.

(iii) Consideration of your comments and updated dossier

You submitted a dossier update on 07 October 2016 (submission number [redacted]). In your update you have added a document entitled "[redacted] (date on 06 October 2016) in IUCLID section 13. In this document related to aquatic toxicity testing you state: *"New short-term data with appropriate analytics will be added to the current data-set. The new data will be used to re-evaluate the current data set and determine potential data gaps. Also, it is expected that the new data will allow for a conclusion regarding the question of which organism is the most sensitive species. Based on the outcome, and taking into account the ECHA integrated test strategy, the most relevant species to perform long-term tests with will be determined. Based on the current data-set, it is expected that the relevant follow-up will be the daphnia reproduction toxicity test. Furthermore, the most relevant analogue, or analogues to perform long-term tests with will be determined."*

ECHA acknowledges your strategy for generating the new data and your aim to follow the ECHA's integrated testing strategy as described in this decision.

(iv) Conclusion

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the following additional tests using the registered substance subject to the present decision as listed above:

4. Short-term toxicity testing on aquatic invertebrates (test method: Acute immobilisation on Daphnia, OECD TG 202 / EU C.2)
5. Growth inhibition study on aquatic algae and cyanobacteria (test method: Algal inhibition test, OECD TG 201 / EU C.3)
6. Short-term toxicity testing on fish (test method: Acute toxicity test to Fish, OECD TG 203 / EU C.1)
7. Long-term toxicity testing on aquatic invertebrates (test method: Daphnia magna Reproduction Test (EU C. 20 / OECD TG 211).

Appendix 2: Procedural history

ECHA received your registration containing the testing proposal(s) for examination pursuant to Article 40(1) on 14 November 2014.

ECHA held a third party consultation for the testing proposal(s) from 16 March 2015 until 30 April 2015. ECHA did not receive information from third parties.

You were initially notified that the draft decision does not take into account any updates after 8 August 2016. However, following your request and justification provided (including the complexity of the category involving additional two substances), ECHA has exceptionally granted you additonal two months for the update. Your update of 7 October 2016 with submission number YZ643572-88 was subsequently taken into account when processing this decision.

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

ECHA notified the draft decision to the competent authorities of the Member States for proposals 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 decision does not imply that the information provided in your registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the 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 the Member States.

3. In carrying out the test(s) required by the present decision it is important to ensure that the particular sample of substance tested 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. If the registration of the substance covers different grades, the sample used for the new test(s) must be suitable to assess these. Furthermore, 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.