ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 22 November 2018

Addressee: [redacted]

Decision number: CCH-D-2114449810-49-01/F
Substance name: ETHYLDIISOPROPYLAMINE
EC number: 230-392-0
CAS number: 7087-68-5
Registration number: [redacted]
Submission number: [redacted]
Submission date: 25 August 2015
Registered tonnage band: 100-1000

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. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD 421/422) in rats, oral route with the registered substance;**

2. **Sub-chronic toxicity study (90-day), inhalation route (Annex IX, Section 8.6.2.; test method: OECD TG 413) in rats with the registered substance;**

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

4. **Robust study summary (RSS) for key study, "[redacted] (2005)/K1KS/Toxicity to aquatic algae and cyanobacteria", Aquatic toxicity, Growth inhibition study aquatic plants (Annex VII, Section 9.1.2 in conjunction with Annex I, Section 3.1.5);**

   or

   Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: Alga, growth inhibition test, EU C.3./OECD TG 201) with the registered substance;

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;**

7. Classification and labelling (Annex VI, Section 4.): Apply classification and labelling on the registered substance for long-term aquatic hazard or provide a justification for not classifying.

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 to the REACH Regulation. 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 adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by ***31 May 2021***. You also have to 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 and 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, has to 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 Ofelia Bercaru, Head of Unit, Evaluation E3

[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.

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Appendix 1: Reasons

HUMAN HEALTH INFORMATION

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Your registration dossier contains for multiple endpoints adaptation arguments in the form of a grouping and read-across approach under Annex XI, Section 1.5. of the REACH Regulation. ECHA has considered first the scientific and regulatory validity of your read-across approach in general before assessing the individual endpoints (sections 1-3)

Grouping and read-across approach for toxicological information

You seek to adapt the information requirements for a screening study for reproductive/developmental toxicity (Annex VIII, 8.7.1.), a sub-chronic toxicity (90-day) study (Annex IX, Section 8.6.2.) and pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) by applying a read-across approach in accordance with Annex XI, Section 1.5.

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural aspects the chemical structures have in common and the differences between the structures of the source and registered substances[2]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Thus physicochemical properties influence the human health and

[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.

environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[3]- (1) (Bio)transformation to common compound(s) and (2) Different compounds have the same type of effect(s).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

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

You propose read-across between the four structurally similar substances listed below as source substances and the substance subject to this decision, ethyldiisopropylamine (EDIPA) (EC 230-392-0) (CAS No 7087-68-5) as target substance.

- N,N-dimethylmethanamine (TMA), CAS No 75-50-3
- N,N-diethylethanamine (TEA), CAS No 121-44-8
- N,N-dibutylbutan-1-amine (TBA), CAS No 102-82-9

Your dossier contains read-across documentation in the Chemical Safety Report (CSR) and in section 13.2 of the IUCLID technical dossier.

You use the following arguments to support the prediction of properties of the registered substance from data for reference substance(s) within the group by interpolation to other substances in the group: all the substances within the group are tertiary amines with only aliphatic organic substituents, are composed of only carbon, hydrogen and nitrogen, have a molecular weight of less than 200 Daltons and exhibit a consistent incremental change in their structure in the form of an increasing number of carbon atoms. You consider that the "*high electronegativity and lone pair of lectrons associated with the nitrogen underly the chemical behaviour of these tertiary aliphatic amines and stress that the alkalinity is associated with the corrosivity of these compounds is "a general feature of the compounds*". You further state that "*the alkyl group may include a group that will not react with or substantially affect the properties of the amine function*" and point out that "*there is commonality in the metabolism of the tertiary amines*".

You conclude that the "*observed corrosive properties overwhelm the systemic toxicity of the tertiary amines in most cases*" and that "*the known acute oral and dermal effects are generally related to the alkaline properties and are expected to be a general feature of the category*". According to you the source and registered substances have similar properties for the above-mentioned information requirements.
ECHA considers that this information is your read-across hypothesis, which provides the basis whereby you predict the properties of the registered substance from the source substances.

[3] Please see ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

ii. ECHA analysis of the grouping and read-across approach

ECHA considers that your read-across hypothesis is based upon the claim that these tertiary amines have corrosive properties which are claimed to limit the relevance of systemic toxicological properties and on the consideration that the linear alkyl groups will not react and do not affect the properties of the amine function. You also state that there is a common metabolism pathway among the substances included in this read-across approach.

Based on the information provided in your registration dossier, ECHA observes that the properties of the source and the registered substance differ, as outlined below. Specifically, whilst your read-across hypothesis is that the source and target substances have corrosive properties which are claimed to limit the relevance of systemic toxicological properties, ECHA observes that you have reported in your read-across justification that *"TMA and TEA are corrosive to the skin, but EDIPA and TBA are only irritating"*. In line with this statement, you report in your technical dossier that the target substance has *"moderately irritating"* properties. You did not consider that these properties were fulfilling the criteria for classification for skin irritation or corrosion as evidenced by the absence of classification for these hazards in your self-classification of the substance reported in section 2.1 of the technical dossier. ECHA points out that the source substance TMA has a harmonised classification as Skin Irrit. 2 (Index Number 612-001-00-9) and that the source substance TEA has a harmonised classification as Skin Corr. 1A (Index Number 612-004-00-5).

In view of these differences in the potential of the source and target substances to elicit skin irritation or corrosion, the information provided in the dossier contradicts your read-across hypothesis that the properties of the source and registered substances are similar, that these tertiary amines have corrosive properties which are claimed to limit the relevance of systemic toxicological properties and that the linear alkyl groups will not react and do not affect the properties of the amine function. Accordingly, your read-across hypothesis is not a reliable basis whereby the properties of the registered substance may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group.

Furthermore, there is insufficient information in the registration dossier to support the claim in your read-across hypothesis that the linear alkyl groups will not react and do not affect the properties of the amine function.

A prerequisite for a prediction based on read-across is that the substances involved are structurally similar and are likely to have similar properties or follow a regular pattern. One important aspect in this regard is the data matrix comparing properties of source and target substances. ECHA considers that the available evidence is not sufficient to conclude on the similarity between the target and source substances regarding systemic toxicity. With respect to the information requirements addressed in this read-across, you have reported information from the analogue substances TMA and TEA for repeated-dose toxicity, from TMA only for toxicity to reproduction and from TBA only for pre-natal developmental toxicity. There are no reliable experimental evidence with the target substance to allow comparison with the source substances regarding systemic toxicity.

You have also claimed that the different alkyl groups will not impact the toxicological properties of the source and target substances. As indicated above, the data set reported in the technical dossier does not include data neither informing on the toxicological properties of the target substance after repeated administration nor on its reproductive and

developmental toxicological properties. ECHA also notes that the source substances TBA and TMA do exhibit similar maternal toxicity at comparable doses in the pre-natal developmental toxicity study [redacted] 1991) and in the reproductive/developmental toxicity screening test [redacted], 2003) conducted in rats via the oral route, both substances causing death in the high dose groups. However, this is an unspecific finding which may have numerous possible causes and cannot be considered as a reliable basis to establish that toxicological properties are similar. Furthermore, pre-natal developmental toxicity studies are not designed to investigate systemic toxicity. In particular, the investigations are restricted to pregnant females and do not include the parameters included in the OECD test guideline for repeated dose toxicity such as the test guideline 408. A comparison on the basis of results obtained in pre-natal developmental toxicity studies may provide useful information for this information requirement and for the substances tested. However, a similar toxicity between TBA and TMA in this regard cannot lead to the conclusion that there would be also similar toxicity between TBA or TMA and the registered substance, since there are no data available on the registered substance. Therefore ECHA considers that you have not provided any experimental information or other adequate and reliable information establishing that these structural differences do not affect the toxicological properties of the target and source substances for the endpoints under consideration.

Similarly, you indicate that there "*is a commonality in the metabolism of the tertiary amines*" and support this claim by providing robust study summaries of toxicokinetic investigations conducted in humans and rats using the analogue substances TMA and DMEA. Whilst these investigations confirm that N-oxidation is the predominant metabolic pathway for these tertiary amines, ECHA stresses that, as a general, similarity in metabolic pathway does not imply similarity in toxicological properties. As mentioned above, the source and target substances exhibit structural differences and structurally different N-oxides and other metabolites will be formed from these source and target substances. ECHA notes that you have not provided any experimental information or other adequate and reliable information establishing that these structurally different metabolites do not affect the toxicological properties of the target and source substances for the endpoints under consideration.

For the reasons presented above and on the basis of the information provided in your registration dossier, there is not sufficient support for your proposal that the corrosive properties of these substances make systemic toxicological properties of these substance irrelevant. In addition, there is no information to support your assumption that the structural differences among these substances, i.e. their linear alkyl groups, do not affect their toxicological properties for the endpoints under consideration. Moreover, ECHA noted above that the registered substance is not classified as skin irritant. Therefore your argument based on corrosive properties appears to be not relevant for the target substance.

In your read-across justification document you indicate that "*TMA and TEA were evaluated in the frame of the HPV OECD program*". ECHA outlines that making use of grouping of substances and read-across under the REACH Regulation and evaluation of substances in the context of the OECD HPV program are governed by different rules. Therefore the conclusions drawn in the context of the OECD HPV program cannot necessarily be directly applicable under REACH. ECHA further points out that whilst the two source substances mentioned above are members of the OECD category on "Tertiary Amines", the registered substance ethyldiisopropylamine (EC 230-392-0) (CAS No 7087-68-5) is not listed as a member of this category.

In your comments to the draft decision, you have presented a revised adaptation in the form of a "*Tertiary Amines Category*" including three substances: ethyldiisoprpylamine (EDIPA), i.e. the substance subject to this decision, N,N- dimethylisopropylamine (DMIPA – CAS No 996-35-0 – EC No 213-635-5) and N-N-dimethylethylamine (DMEA - CAS No 598-56-1 EC No 209-940-8).

You consider that read-across may be applied within this group of substances "*providing that the toxicological requested studies that will be generated EDIPA, DMIPA, and DMEA will demonstrate comparable toxicological profiles*". You described a testing strategy whereby you plan on using results from an ongoing 90-day study performed with the analogue substance DMEA as source data. You specified that you intend to conduct 7-day and 28-day studies with DMIPA and EDIPA and to compare the outcome of these studies with the results from similar studies conducted with the source substance DMEA.

ECHA observes that you have not explained why only these three tertiary amines have been considered in this grouping approach, other than by referring to the fact that these three substances have been subject to recent compliance checks. You have listed common features shared by the substances involved in your revised read-across in the section on "*analogue approach justification*" on page 6 of your comments. ECHA notes that other substances fulfilling these criteria such as TMA, TBA and TEA which were initially considered in the read-across approach addressed in the draft decision issued to you also exhibit the structural features of tertiary amines but are not included in your revised adaptation. You have not explained why these substances are now disregarded as members of the "*tertiary amine family*".

Further, you have not substantiated your selection of DMEA as the source substance among DMEA, DMIPA and EDIPA other than by indicating that studies are ongoing with DMEA. Finally, the source studies and the supporting information referred to in your comments are not yet available. Therefore, in the absence of all this information, ECHA considers that the revised adaptation as presented in your comments to the draft decision cannot be accepted.

Endpoint-specific considerations on the revised read-across approach included in the comments are provided in the following sections.

iii. Conclusion on the grouping and read-across approach

For the reasons as set out above, ECHA considers that this grouping and read-across approach does not provide a reliable basis whereby the human health effects of the registered substance may be predicted from data for reference substance(s) within the group. Hence, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation. ECHA notes that there are specific considerations for the individual endpoints which also result in a failure to meet the provisions of Annex XI, 1.5, and these are set out under the endpoint concerned.

As described above, further elements are needed to establish a reliable prediction for toxicological properties, based on recognition of the structural aspects the chemical structures have in common and the differences between the structures of the source and registered substances. This could be achieved (if it is possible) by a well-founded hypothesis of (bio)transformation to a common compound(s), or that the registered and source substance(s) have the same type of effect(s), together with sufficient supporting information to allow a prediction of human health properties.

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1. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

"Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. No such evidence is presented in the dossier. Therefore, 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 screening for reproductive/developmental toxicity in the dossier that would meet the information requirement of Annex VIII, Section 8.7.1.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) with the analogue substance N,N-dimethylmethanamine (TMA) (EC no 200-875-0). However, as explained above in Appendix 1, section on "*Grouping and read-across approach for toxicological information*", your adaptation of the information requirement is rejected.

Therefore, 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 methods OECD TG 421/422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with 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 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. 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 referred to the adaptation possibility listed in Annex VIII, 8.7.1 column 2 whereby the screening for reproductive/developmental toxicity study does not need to be conducted in case a pre-natal developmental toxicity study is available.

ECHA notes that no data from a pre-natal developmental toxicity study is currently available and included in the registration dossier of EDIPA. From the information provided in the comments to the draft decision, ECHA understands that you indicated your agreement to conduct a pre-natal developmental toxicity study with the registered substance, EDIPA. However, since the results of this study are not yet available, the conditions for waiving the information requirement fo Annex VIII, 8.7.1 for a screening for reproductive/developmental toxicity study according to the adaptation possibility listed in Annex VIII, 8.7.1 column 2 are not met.

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: Reproductive/developmental toxicity screening test (test method: OECD TG 421) *or* Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

Notes for your considerations

For the selection of the appropriate test, please consult ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.5 and 7.6 (version 6.0, July 2017).

The registrant should also carefully consider the order of testing especially the requested screening (OECD TG 421/422) and the developmental toxicity studies (OECD TG 414) to ensure unnecessary animal testing is avoided, paying particular attention to the end point specific guidance (https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf) Section R.7.6.2.3.2., pages 484 to 485 of version 6.0 – July 2017."

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

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 information on the following studies:

Oral route:
1. Amoore, 1978, Key study, 84-day repeated dose toxicity study conducted in rats via the oral route (feed) using N,N-dimethylmethanamine (TMA);
2. [redacted] 2003, Supporting study, Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) conducted in rats via the oral route (gavage) using N,N-dimethylmethanamine (TMA).

Inhalation route:
3. Lynch, 1990, Key study, 28-week repeated dose toxicity study conducted in rats via the inhalation route using N,N-diethylethanamine (TEA);
4. Kinney, 1990, weight of evidence, 14-day repeated dose toxicity study conducted in rats via the inhalation route using N,N-dimethylmethanamine (TMA).

However, as explained above in Appendix 1, section on "*Grouping and read-across approach for toxicological information*", the read-across adaptation using TMA and TEA as source substances is rejected.

ECHA makes the following observations on the above-mentioned studies:

1. Amoore, 1978: This study is flagged as key study in the technical dossier for the endpoint repeated dose toxicity. According to the provisions of Annex XI, Section 1.5 of the REACH Regulation, the results of the read-across adaptation should have "adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3)". The OECD test guideline 408 is the corresponding test method. Based on the information reported in the endpoint study record, it appears that the design of the study conducted by Amoore et al. significantly differs from the recommendations of the OECD test guideline 408. Specifically, the study by Amoore *et al.* was conducted in males only, with only 5 animals per test group and the level of information reported in the technical dossier is insufficient to assess the nature of the investigations conducted as part of this study. Therefore, ECHA considers that this source study does not fulfil the requirement of Annex XI, Section 1.5 of the REACH Regulation for an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3).

2. [redacted] 2003: this study was conducted according to the OECD test guideline 422 and according to the good laboratory practices. Therefore, ECHA considers that it provides reliable information on the properties of the analogue substance TMA. However, the study duration and the scope of the investigations conducted in accordance with the OECD test guideline 422 do not provide an adequate and reliable coverage of the key parameters addressed in the OECD test guideline 408. Therefore this study cannot be used as key study in a read-across approach intended to fulfil the information requirement of Annex IX, Section 8.6.2. for a sub-chronic toxicity study (90 day). ECHA also stresses that no explanation for the death of 3 animals in the high dose group of this study is provided in the technical dossier.

4. Kinney, 1990: this study has been flagged by you as part of a weight of evidence approach for the repeated dose toxicity of the registered substance after inhalation exposure. Based on the information provided in the technical dossier, ECHA considers that this study provides relevant information on the local toxicity observed with repeated inhalation exposure to the analogue substance TMA. However, the level of information reported prevents concluding on the nature and adequacy of the investigations on systemic toxicity conducted as part of this study. Specifically, it cannot be determined which organs and tissues have been subject to histopathology and which clinical and biochemistry parameters were investigated. Therefore, ECHA considers that the information obtained from this study, as currently reported, cannot be used in a weight of evidence approach to determine whether the registered substance has or has not dangerous systemic properties after repeated inhalation exposure as required under Annex XI, Section 1.2 of the REACH Regulation.

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
Since the registered substance is a liquid of high vapour pressure (14.25 hPa at 20°C) classified as STOT SE 3 for the respiratory tract and human exposure by the inhalation route is reported in the registration dossier, ECHA considers that the inhalation route is the most appropriate route of administration. Testing via the inhalation route will inform on possible systemic toxicity of the registered substance via the relevant route of exposure for humans

and will also provide quantitatve information on the potential of this substance to cause local toxicity after repeated exposure. Hence, the test shall be performed by the inhalation route using the test method EU B.29./OECD TG 413.

According to the test method OECD TG 413 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

In your comments to the draft decision, you have presented a revised adaptation for this information requirement in the form of a "T*ertiary Amines Category*" which "*may be applied providing that the toxicological requested studies that will be generated EDIPA, DMIPA, and DMEA will demonstrate comparable toxicological profiles*". You also described a testing strategy whereby you plan on using results from an ongoing 90-day study performed with the analogue substance DMEA as source data. You specified that you intend to conduct 7-day and 28-day studies with EDIPA (the registered substance) and DMIPA (CAS No 996-35-0 – EC No 213-635-5) and to compare the outcome of these studies with the results from similar studies conducted with the source substance DMEA.

ECHA notes that the adaptation reflected in the comments based on a grouping of DMEA, EDIPA and DMIPA differs from the read-across approach included in the submission subject to this compliance check and addressed in the draft decision as indicated in the response to your comments in "*ECHA analysis of the grouping and read-across approach*". Whilst the proposed testing plan may support adaptations based on Annex XI, Section 1.5 in the future, ECHA points out that neither the source data nor the supporting information mentioned in your comments is available yet. Furthermore, you did not provide criteria which would determine whether there are indeed "*comparable toxicological profiles*". In that respect, ECHA considers that the following criteria are decisive for the actual determination of similarity in toxicity:

- No adverse effects are observed in any organ or tissue for the both source and target substances when tested up to the limit dose; or

- Comparable effects (i.e. in terms of type of effect, severity and incidence) are observed in the same organ(s) tissue(s) or parameters at similar dose level for both source and target substances.

Verifying that these criteria are met is an essential condition for the valid justification of the similarity of toxicity for the substances covered by the category and, hence, for meeting the provisions in Annex XI, Section 1.5 to adapt the information requirement.
ECHA also observes that you have neither provided considerations nor outlined your plans on how to comply with the REACH Regulation in case the proposed read-across hypothesis is not confirmed by the data proposed to be generated.

Based on the information currenty provided, ECHA concludes that the proposed adaptation cannot be accepted. Your proposal to postpone the decision is discussed at the end of this Appendix under "Deadline to submit the requested information in this 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: Sub-chronic inhalation toxicity: 90-day study (test method: OECD TG 413) in rats.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "pre-natal developmental toxicity study" (test method 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 record for a pre-natal developmental toxicity study (OECD TG 414) with the analogue substance(s) N,N-dibutylbutan-1-amine (TBA) (EC no 203-058-7) ([redacted], 1991). However, as explained above in Appendix 1, section on "*Grouping and read-across approach for toxicological information*", the read-across adaptation using TBA as source substance is rejected.

Therefore 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 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 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Although you have not provided endpoint specific comments, ECHA understands from table 4 of your comments to the draft decision that you expressed agreement with ECHA's request for a pre-natal developmental toxicity study 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: OECD TG 414) in a first species (rat or rabbit) by the oral route.

ECOTOXICOLOGICAL INFORMATION

4. Robust study summary (RSS) for key study, "[redacted] (2005)/K1KS/Toxicity to aquatic algae and cyanobacteria", Aquatic toxicity, Growth inhibition study aquatic plants (Annex VII, Section 9.1.2 in conjunction with Annex I, Section 3.1.5);

or

Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: Alga, growth inhibition test, EU C.3./OECD TG 201) with the registered substance;

Pursuant to Articles 10(a)(vii) of the REACH Regulation, the information set out in Annexes VII to XI must be provided in the form of a robust study summary, if required under Annex I. Article 3(28) of the REACH Regulation defines a robust study summary as a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study minimising the need to consult the full study report. Guidance on the preparation of the robust study summaries is provided in the ECHA Practical Guide 3: 'How to report robust study summaries'.

"Growth inhibition study aquatic plants" is a standard information requirement as laid down in Annex VII, Section 9.1.2. 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. Furthermore, pursuant to Article 10(a)(vii) and Annex I, Section 3.1.5. of the REACH Regulation the study giving rise to the highest concern shall be used to draw the conclusion and a robust study summary shall be prepared for that study and included as part of the technical dossier. A Robust study summary will be required of all key data used in the hazard assessment.

In the technical dossier you have provided the following study record to fulfil the standard information requirement of Annex VII, Section 9.1.2.: Key study, reliability 1, "[redacted] (2005)/K1KS/Toxicity to aquatic algae and cyanobacteria", GLP compliance: yes, test method: according to OECD Guideline 201 (Alga, Growth Inhibition Test)/EU Method C.3 (Algal Inhibition test) with the registered substance.

ECHA notes that in the RSS you have indicated that the validity criteria of the study have been fulfilled. However, ECHA considers that you have not provided sufficient information in the RSS, or elsewhere in the technical dossier, to allow verification of the validity of this study, as further discussed below.

According to the validity criteria described in OECD TG 201, par. 11, a test is valid when (1) the biomass in the control cultures increased exponentially by a factor of at least 16 (corresponds to a specific growth rate of 0.92/day) within the 72-hour test period; (2) the mean coefficient of variation for section-by-section specific growth rates (days 0-1, 1-2 and 2-3, for 72-hour tests) in the control cultures must not exceed 35%; (3) the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures must not exceed 7% in tests with *Pseudokirchneriella subcapitata*.

Concerning these validity criteria, in the RSS you only report: "*increase in cell density in control solution greater than a factor of 16 (R = 82)" and "final concentrations maintained within the designated limit of 80% of the initial concentrations in non inoculated flasks.*" ECHA notes that the last one is not one of the validity criteria as given in par. 11 of OECD TG 201. In addition, ECHA notes that in your RSS you have not provided information on biomass in the control cultures during the test. In absence of this information, it is not possible for ECHA to evaluate whether the validity criteria of this study described in OECD TG 201 have been fulfilled.

Furthermore, ECHA notes that this study deviates from the standard OECD TG 201 since only four concentrations were used in this study ("*Nominal concentrations in the definitive test: 0-250-100-200-400 mg/L*"), whereas at least 5 concentrations should be selected in the definitive test according to par. 22 of OECD TG 201. ECHA notes that you have neither provided statistical analysis of the results, nor have you described whether this deviation from the standard guideline affected the reliability of the results. In the absence of this information, it is not possible for ECHA to evaluate the reliability of this study.

ECHA notes that, contrary to Article 3(28) of the REACH Regulation the documentation of the study is insufficient and does not allow an independent assessment of the adequacy of the study, its results and use for hazard assessment. In particular, in addition to the above, the following elements are not reported:

a. test medium;
b. observations in the controls and treated cultures;
c. determination of growth rates in the controls and treated cultures;
d. determination of the mean coefficient of variation for section-by-section specific growth rates (days 0-1, 1-2 and 2-3, for 72-hour tests) in the control;
e. determination of the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures;
f. other effects (frond and root size and appearance, necrosis, chlorosis, gibbosity, loss of buoyancy, etc.);
g. EC50, EC10 or NOEC and LOEC at the different reporting timings, dose-response relationships, description of statistical analysis performed.

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.

In your comments to the draft decision, you have provided further information on this algae growth inhibition study and have agreed to update the robust study summary accordingly. You have also provided a new statistical analysis based on the data available in the original study report, in order to obtain the missing information on the validity criteria.

Based on the information provided in Annex 1 of your comments, ECHA acknowledges that the validity criteria of OECD TG 201 have been fulfilled in the controls: (1) biomass increased by a factor of 81,7 and specific growth rate was 1.464/day; (2) mean coefficient of variation over time was 19.9%; (3) coefficient of variation of average specific growth rates was 4%. ECHA notes that this information allows to verify that the study is valid and that this information should be included in the technical dossier.

You have provided the following justification regarding the use of four test concentrations instead of the five required in par. 22 of OECD TG 201: "*the spacing factor (2.0) used in this study is quite narrow. In addition, the lowest concentration tested gave almost no inhibition (4.5%), while the next concentration gave 17.9% inhibition, followed by 36.8% for the third concentration. The highest tested concentration gave almost complete inhibition (93.5%). Therefore, all four tested concentrations play a mathematical role in the derivation of the ErCx. It is not rare that in aquatic toxicity studies, the fifth tested concentration does not play any mathematical role because it has the same effect as the lowest or highest tested concentration (i.e., almost 0 or 100% inhibition). The registrants therefore consider that in*

this case where four actively modelling concentrations have been tested with a narrow spacing factor, the results are robust and accurate." You also indicate that following the new statistical analysis "*new 72h-ErC50 and 72h-ErC10 based on growth rate inhibition were derived. These are higher (albeit of the same order of magnitude) than those stated in the study report.*" Based on the statistical analysis provided, ECHA considers that a statistically significant dose-response was obtained with the tested concentrations, hence ECHA considers that you have adequately justified that the deviation regarding the number of tested concentration did not affect the reliability of the results. ECHA notes that this justification allows to verify that the results are reliable and should be included in the updated RSS. Furthermore, ECHA agrees that the results derived following the new statistical analysis are acceptable and should be included in the updated RSS (for growth rate: 72h EC50 = 196.283 (144.357-264.266) mg/L, 72h EC10 = 118.983 (91.4-154.89) mg/L and NOEC = 32 mg/L).

Finally, ECHA notes that you have provided information on the elements listed above in points *a* to *g* required to assess the adequacy of the study. ECHA considers that this information allows to verify that the study is adequate and should be included in an updated RSS as also indicated by you.

ECHA hence acknowledges that based on the further information provided in your comments the algae growth inhibition study can be considered valid and adequate. However, this information needs to be included in the technical dossier in the formats requested by the REACH Regulation. While for the purpose of this decision making, ECHA does not take into account any dossier updates after the notification of this draft decision under Article 50(1) of the REACH Regulation, ECHA notes that dossier updates and any adaptations therein will be evaluated by ECHA at the follow up stage. Therefore the request(s) remains in the draft decision.

In order to allow an independent assessment of the study submitted, pursuant to Article 41(1) and (3) of the REACH Regulation you are requested to provide complete robust study summary with the above missing elements for the key study.

Alternatively, if you cannot submit a complete RSS or the RSS indicates that the study is not reliable and not adequate to fulfil the information requirement, 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: Algae growth inhibition test, EU C.3./OECD TG 201.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"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 sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a *Daphnia magna* Reproduction Test ([redacted] 2013, key study, reliability 1, GLP, test method: OECD TG 211, results: 21d NOEC = 1.73 mg/L) with the analogue substance n,n-dimethylisopropylamine (EC no 213-635-5)].

You propose read-across between the structurally similar substance, n,n-dimethylisopropylamine (DMIPA) (EC No 213-635-5, CAS No 996-35-0) as source substance, and the substance subject to this decision, ethyldiisopropylamine (EDIPA, EC No 230-392-0, CAS No 7087-68-5) as target substance.

Your dossier contains read-across documentation as a separate attachment in Section 13 of the IUCLID technical dossier "[redacted]

You use the following arguments to support the prediction of properties of the registered substance from data for the source substances:

- Target and source substances have high purity (>99%) and the low levels of impurities are not expected to influence the prediction.
- Target and source substances are tertiary amines with only aliphatic organic substituents, are composed of only carbon, hydrogen and nitrogen, have a molecular weight of less than 200 Daltons and exhibit a consistent incremental change in their structure in the form of an increasing number of carbon atoms.
- "[redacted]."
- "*both substances have similar behaviour in the environment and have similar bioavailability.*"

You conclude that "*Taking into account the structure similarity, the physico-chemical and environmental fate prperties, and ecotoxicological effects between DMIPA and EDIPA, it seems appropriate to apply a read-across for the chronic daphnia test.*" According to you the target and the source substances have similar properties for the endpoint long-term toxicity to aquatic invertebrates.

ECHA considers that this information is your read-across hypothesis for this one-to-one analogue approach, which provides the basis whereby you predict the properties of the registered substance from the source substances.

ECHA has evaluated the information and documentation provided in the registration dossier in light of the requirements of Annex XI, Section 1.5 of the REACH Regulation. According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

In the following, ECHA examines whether the substances have indeed similar properties and whether long-term toxicity on aquatic invertebrates for the target substance can be predicted from the source substance.

ECHA agrees that the two substances are structurally similar and their chemical structures differ in the number of C atoms in the alkyl group. You consider that this difference in alkyl group will not impact the properties of the source and target substance. However, source and target substances are relatively small molecules and therefore a difference of 3 carbon atoms in the alkyl group is substantial and might lead to significant differences in the properties.

ECHA observes that there is insufficient information in the registration dossier to support the claim in your hypothesis that the difference in alkyl group will not impact the properties of the source and target substance.

A prerequisite for a prediction based on read-across is that the substances involved are structurally similar and are likely to have similar properties or follow a regular pattern. One important aspect in this regard is the data matrix comparing properties of source and target substances.

ECHA acknowledges that your read-across justification document includes a summary of some key physico-chemical and environmental fate and pathway properties, as well as a data matrix for ecotoxicity properties, allowing a comparison of these properties between the target and the source substances.

ECHA agrees that the target and source substances have similar physico-chemical properties and that they are not ready biodegradable. ECHA also agrees that both substances are expected to dissociate in water at environmentally relevant pHs and to be stable to hydrolysis. However, ECHA also notes that based on the difference in chemical structure (number of C atoms in the alkyl groups), the target substance EDIPA is expected to have a higher Log Kow than the source substance DMIPA. Although the bioaccumulation potential for both substances is indeed likely very low, there might be differences in bioavailability in the ecotoxicity tests as well as differences in uptake potential that could influence ecotoxicity. In general, longer alkyl chains (higher Log Kow) lead to higher bioavailability and uptake potential; this may lead to higher concentrations at the toxic site of action and hence may cause more severe effects. In this particular case, the target substance could be more toxic than the source substance. ECHA considers that you have not provided any adequate and reliable information addressing how and why the potentially higher LogKow of the target substance does not affect the ecotoxicological properties of the target and source substances for the endpoint under consideration.

Regarding ecotoxicity properties, you have claimed that there is no difference in species sensitivity between the target and the source substances, since "*As already observed for the linear alkyl amines, fish are less sensitive compared to algae and daphnia*". While you have not provided any evidence or reference for this general statement, ECHA notes that this is confirmed by the short-term aquatic toxicity data available on the target substance EDIPA. However, ECHA also notes that the validity of the algae study on the target substance EDIPA cannot currently be assessed, as described in request 4. Based on your comments to the draft decision this algae study can be considered valid, as discussed in request 4 above. However, the data does still not allow to conclude that fish is the least sensitive species

since the EC50 value of the algae study is higher than the highest tested concentration in the short-term fish study. In addition, ECHA observes that for the source substance DMIPA it is not possible to compare the sensitivity between fish and *Daphnia* in short-term studies, since no effects were observed at the tested concentrations (unbounded effect value). Therefore, your general statement that for linear alkyl amines fish is the least sensitive species is not supported by the data in the data matrix for DMIPA. As a consequence, ECHA considers that there is insufficient information to allow comparison between the target and the source substance regarding species sensitivities in short-term aquatic toxicity studies.

Furthermore, based on the information provided in your registration dossier, ECHA observes that the ecotoxicological properties of the substances differ, as outlined below. ECHA agrees that the target and the source substances would have a similar mode of toxic action since both contain the same reactive functional group (i.e. tertiary amine). However, ECHA notes that the available evidence does not support similarity between the target and source substances regarding the magnitude of the ecotoxicological effects. ECHA notes that ecotoxicity data is available and presented in the data matrix for several short-term aquatic endpoints (Table 3 of the read-across justification document). However, the only endpoint where a meaningful comparison between source and target substances is possible is short-term toxicity to aquatic invertebrates. The studies on other endpoints either show no effects in neutralised media at the tested concentrations for source and target substances (i.e. short-term toxicity to fish) or they may have not been performed in the same pH conditions (e.g. the algae study on the source substance has no information on pH adjustment, whereas pH was adjusted in the algae study on the target substance). Therefore, results of those studies of source and target substances on other endpoints cannot be compared. ECHA notes that the only endpoint where the aquatic toxicity of target and source substance can be compared – i.e. short-term toxicity to *Daphnia,* where the 48h EC50 values of source and target are >62.5 mg/L and 28.1 mg/L, respectively - indicates that the target substance is more toxic than the source substance.

In view of this difference in short-term toxicity to aquatic invertebrates, the information provided in your dossier contradicts your read-across hypothesis that the properties of the source and registered substances are similar and that the difference in alkyl group does not affect the properties of the amine function. Accordingly, your read-across hypothesis is not a reliable basis whereby the properties of the registered substance may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group.

For the reasons presented above and on the basis of the information provided in your registration dossier, there is not sufficient support for your assumption that the structural differences among these substances, i.e. their alkyl groups, do not affect their ecotoxicological properties for the endpoint under consideration. As a consequence, ECHA considers that this grouping and read-across approach does not provide a reliable basis whereby the long-term toxicity on aquatic invertebrates for the registered substance may be predicted from data for reference substance(s) within the group. Hence, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation.

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 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.

In your comments to the draft decision you agree to perform the long-term aquatic invertebrates study requested in this decision and have detailed the testing strategy you intend to follow to determine whether the long-term fish study (request 6. below) is additionally needed. Your comments regarding the testing strategy for aquatic toxicity testing have been addressed under request 6. 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: Daphnia magna reproduction test (test method: EU C.20./OECD TG 211).

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"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.

You have sought to adapt this information requirement according to Annex IX, Section 9.1.6., column 2. You provided the following justification for the adaptation: "*Taking into consideration results from short-term toxicity tests on fish, Daphnia and algae, there is a high probability that the most sensitive species (daphnia) has already been examined and that a further long-term result from fish would not be lower than the data already available. Moreover, the exposure levels estimated in all relevant scenarios do not exceed the appropriate PNEC (all risk characterization ratios are under 1.0), and the likelihood and severity of an event occurring due to the physicochemical properties of the substance in the aquatic environment are negligible. Therefore, and for reasons of animal welfare, a chronic test on fish is not provided. In conclusion: In accordance with column 2 of REACH Annex IX, the long term testing on fish does not need to be conducted as the chemical safety assessment according to Annex I has not indicated a need to investigate further the effects on aquatic organisms.*"

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.6., column 2 for the following reasons.

In your adaptation you refer to the relative species sensitivity in acute toxicity tests. ECHA notes that based on the available acute aquatic toxicity data on the registered substance, there is no compelling evidence to suggest that the fish value is likely to be at least a factor of 10 less sensitive than invertebrates or algae, since only an unbounded value is available

for short-term toxicity to 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.

You concluded in your current chemical safety assessment (CSA) attached to your technical dossier, that the risks are controlled based on data provided for acute toxicity on all three trophic levels and long-term toxicity on algae and aquatic invertebrates. Based on the results of the CSA, you consider that long-term toxicity testing in fish is not needed since "*the exposure levels estimated in all relevant scenarios do not exceed the appropriate PNEC (all risk characterization ratios are under 1.0)*" and since "*...the most sensitive species (daphnia) has already been examined and that a further long-term result from fish would not be lower than the data already available.*" ECHA notes that such conclusion for no risk is currently not valid due to the following reasons:

- The risk assessment you refer to in your adaptation is based on a PNEC with an assessment factor of 10, justified by the following "*Short-term toxicity data are available for primary producers, invertebrates and fish in freshwater. In addition, long-term toxicity data are available for algae and daphnia that can be considered as the most sensitive species. Indeed, toxic effects have been observed for daphnia (EC50 of 28.1 mg/L) and algae (ErC50 of 150 mg/L and ErC10 of 52 mg/L) whereas no mortality of fish was showed at 69.7 mg/L in a limit test. Taking into account acute tests, we can consider that chronic data are available on the most sensitive species, algae and daphnia. In addition, based on intrinsic properties of ethyldiisopropylamine (high water solubility and low log Pow), the substance is not expected to bioaccumulate in organism tissues. Thus an assessment factor of 10 is justified and is applied on the lowest NOEC value, corresponding to 1.73 mg/L for daphnia.*"

  ECHA notes that according to ECHA *Guidance on information requirements and chemical safety assessment (May 2008), Chapter R10 (Section R.10.3.1.2, including Table R.10-4)*, an assessment factor of 10 will normally only be applied when long-term toxicity results (e.g. EC10 or NOECs) are available from at least three species across three trophic levels (e.g. fish, *Daphnia*, and algae or a non-standard organism instead of a standard organism). A data set including long-term toxicity results from aquatic invertebrates and algae would currently merit a use of an assessment factor of 50 based on the ECHA Guidance cited above. An assessment factor of 50 applies to the lowest of two long term results (e.g. EC10 or NOECs) covering two trophic levels when such results have been generated covering that level showing the lowest L(E)C50 in the short-term tests.

  In the absence of long-term toxicity data on fish, ECHA considers that the assessment factor of 10 used in your CSA to calculate the PNEC is not justified and not supported by evidence. Consequently, its use in the CSA is currently not reliable.

- In addition to the previous point, the study on Growth inhibition aquatic plants (Annex

VII, Section 9.1.2.) used in your CSA cannot currently be assessed, as discussed in section 4 above. Consequently, its use in the CSA is currently not reliable.

- The results for Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5) used in your CSA to calculate the PNEC are not valid, as discussed in section 5 above. As a result, also the PNEC derivation and consequent risk characterisation are currently not reliable.

Based on the deficiencies stated above, your risk characterisation is currently not reliable. Therefore, the CSA cannot currently be used to adapt the current information requirement.

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.

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) can be performed 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, Section R.7.8.4.1.*

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).

In the comments to the draft decision, you have provided further information on the algae study so that it can be considered valid (request 4. above) and agreed to carry out the long-term aquatic invertebrates study (request 5. above). Following the long-term *Daphnia* study you would update the CSA and determine whether the long-term fish study requested in this decision is necessary. However, instead of assessment factor (AF) of 50 indicated in ECHA *Guidance on information requirements and chemical safety assessment (May 2008), Chapter R10 (Section R.10.3.1.2, including Table R.10-4)* as an appropriate AF, when valid long-term toxicity data on two trophic levels are available, you consider an AF of 10 appropriate for the PNEC derivation. You consider the use an AF of 10 justified since you consider that for the registered substance the effect value for long-term fish is unlikely to be lower than that for long-term *Daphnia* since invertebrates are likely at least 5 times more acutely sensitive than fish.

ECHA points out that the justification to use a lower AF of 10 is not supported by evidence. Your argument to use the lower AF than recommended is based on an assumption that

Daphnia is the most sensitive species in the chronic studies since it is found to be the most sensitive species in the acute studies. ECHA notes that the AFs are designed not only to cover variation arising from interspecies differences in sensitivity but also from extrapolation from acute to chronic effects, which is by nature species/endpoint specific.

An acute-to-chronic ratio cannot be assumed to be standard across species for several reasons. Firstly, acute and chronic studies for fish and *Daphnia* cover different exposure times and endpoints. The measured effects in acute studies are mortality in 96-h for fish and immobilisation in 48-h for *Daphnia*, while in chronic studies potential toxicity is evaluated within longer time periods by different sublethal endpoints, such as hatching and growth for fish in >28-d (depending on the species) and time to first brood and number of offspring produced per female for *Daphnia* in 21 days. Thus, due to the different duration and endpoints measured, the acute-to-chronic ratio for *Daphnia* may be different than that for fish. Secondly, mode of action of a substance may influence some species/endpoints more than others and this sensitivity may not be detected in acute studies alone. For instance, for the structurally similar source substance proposed for the read-across approach (see request 5 above), no effects in acute studies (immobility) were observed for *Daphnia* up to a concentration of 62.5 mg/L (pH neutralised) after 48h, whereas effects in chronic studies (reproduction) where observed at low concentrations leading to a NOEC of 1.73 mg/L (pH neutralised), which may be due to a different mode of action under acute versus chronic effects. Although the read-across for long-term *Daphnia* was rejected, mainly due to it not being conservative as based on available information target is more toxic than the source, ECHA acknowledged that the source and the target substance may have similar modes of action due to similar functional groups (see request 5 above). Hence, since as shown in the studies with the proposed source substance chemicals may have different modes of action under acute and chronic studies, species sensitivity in acute studies is not always a meaningful indication of the sensitivity in chronic studies. You have not explained whether a lower AF would take into account such potential differences in acute and chronic effects (e.g. related to mode of action, species and endpoint specific). Consequently, your claim that "*a long-term toxicity to fish study has very little probability to yield a smaller NOEC/EC10 than the long-term toxicity study on daphnia*" is not self-evident nor supported by evidence. ECHA hence considers that the use of an AF of 10 instead of 50 is not justified. Furthermore, while you indicate that you would consider whether the long-term fish study is needed following the update of the CSA, in your comments you also state that long-term fish testing is not at all necessary as you consider fish to be less sensitive than aquatic invertebrates and algae. ECHA points out that long-term fish testing is a standard information requirement at Annex IX. According to the aquatic ITS given in Chapter R.7b of ECHA Guidance, if there is no compelling evidence that fish is likely to be at least a factor of about 10 less sensitive than invertebrates or algae, there may be no further requirements for fish testing. However, as explained in the notes for your consideration section below, in this case there is no substantial (i.e. 10 x or more) difference in the sensitivities of fish and daphnia and/or algae.

However, you seem to consider that a factor of 5 difference in sensitivity would be sufficient to waive the current standard information requirement as you indicate that "*since there is a very high probability that daphnia are at least 5 times more acutely sensitive than fish to EDIPA (..) Waiving this study would therefore allow the sparing of hundreds of vertebrates in a study which has a very low likelihood to lower the PNEC*" and that for your substance "*A factor 5 difference (i.e. fish 96h-LC50 equal or higher than 140 mg/L neutralized EDIPA) or more is likely*". In order to support your claim, you also refer to confidence intervals of the

effect values obtained in the acute studies and to a UBA Report ([redacted]) entititled "*Comparison of species sensitivity of Daphnia and fish in acute and chronic testing*" (2014). As a consequence, you conclude that long-term fish testing is not necessary due to the "*very low likelihood to lower the PNEC*".
ECHA does not consider the approach acceptable due to the following. First, based on the acute data provided, the sensitivity difference between fish and *Daphnia* is a factor of at least 2.5. While in the short-term *Daphnia* key study it was possible to derive an effect value, i.e. 48h EC = 28.1 mg/L (measured, 95% CL: 16.7-41.8, pH adjusted), in the short-term fish study no mortality was observed up to a concentration of 69.7 mg/L (measured. pH adjusted) after 96h. Therefore, there is no information available on the possible acute effects in fish above a concentration of 69.7 mg/L. You also recognise this in your comments albeit you report an incorrect concentration value: "*the registrants have no knowledge about the acute toxicity of EDIPA to fish, except that it is above 100 mg/L*". As a consequence, your claim that for the difference in sensitivity "[a] *factor 5 difference (i.e. fish 96h -LC50 equal or higher than 140 mg/L neutralized EDIPA) or more is likely*" is not supported by evidence. Hence, your claim that "*there is a very high probability that daphnia are at least 5 times more acutely sensitive than fish to EDIPA*" is not supported by data.
Second, ECHA acknowledges the information from the UBA report brought forward in your comments, where based on the analysis of acute and chronic fish and *Daphnia* data of about 240 substances from the ECHA and ICS databases it was suggested that the current ITS could be adapted in cases where Daphnia was 5 x more sensitive in acute testing by reducing the sensitivity factor from 10 to 5. In general, ECHA considers that the sensitivity factor of 10 given in ECHA Guidance is adequate to fully cover the uncertainty arising from extrapolating between acute and chronic sensitivies, hence this factor provides an adequate level of environmental protection. Thus, ECHA considers that as per current ECHA Guidance, when no chronic studies are available the sensitivity factor of 10 should be used.

In conclusion, ECHA considers that your specific adaptation for this endpoint is not justified.

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 for requests 5-6

As described above, based on the available acute aquatic toxicity data on the registered substance, there is no compelling evidence to suggest that the fish value is likely to be at least a factor of about 10 less sensitive than invertebrates or algae, since only an unbounded value is available for short-term toxicity to 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.

Due to the substance being ionisable, you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and

ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

7. Classification and labelling (Annex VI, Section 4.): Apply classification and labelling on the registered substance for long-term aquatic hazard or provide a justification for not classifying.

Pursuant to Article 10(a)(iv) of the REACH Regulation your technical dossier shall contain information on classification and labelling of the substance as specified in Annex VI, Section 4 of the REACH Regulation in conjunction with Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures (CLP Regulation).

Annex VI, section 4.1. clarifies that the hazard classification of the substance shall result from the application of Titles I and II of the CLP Regulation. In addition, for each entry, the scientifically justified reasons why no classification is given for a hazard class or differentiation of a hazard class should be provided. According to Article 5(1) of Title I of the CLP Regulation, a substance shall be classified on the basis of available information.

Furthermore, the technical dossier must include the resulting hazard label for the substance in line with Title III of the CLP Regulation (Annex VI, section 4.2 of the REACH Regulation).

According to the CLP Regulation, Annex I, Section 4.1, classification of the substance as hazardous to the aquatic environment recognises that the intrinsic hazard to aquatic organisms is represented by both the acute and long-term hazard of a substance.

For the long-term hazard (Table 4.1.0 (b)), separate hazard categories are defined representing a gradation in the level of hazard identified for (i) Non-rapidly degradable substances for which there are adequate chronic toxicity data available, (ii) Rapidly degradable substances for which there are adequate chronic toxicity data available, and (iii) Substances for which adequate chronic toxicity data are not available and the substance is not rapidly degradable and/or the experimentally determined BCF ≥ 500 (or, if absent, the log Kow ≥ 4). The lowest of the available toxicity values between and within the different trophic levels (fish, crustacean, algae/aquatic plants) shall normally be used to define the appropriate hazard category(ies).

For the long-term hazard, the criteria for classification of a substance into the categories Chronic 1 to 3 follow a tiered approach, as described in Section 4.1.3.3. of ECHA's Guidance on the Application of the CLP Criteria (Version 5.0, July 2017). The first step is to see if available information on chronic toxicity merits long-term (chronic) hazard classification. In absence of adequate chronic toxicity data, the subsequent step is to combine two types of information, i.e. acute aquatic toxicity data and environmental fate data (degradability and bioaccumulation data).

For chronic aquatic toxicity endpoints, there is currently no adequate data available in the technical dossier for long-term toxicity to aquatic invertebrates and long-term toxicity to fish, as described in requests 5 and 6 of this decision, respectively. For algal toxicity, the information provided in the robust study summary does not allow verification of the validity

of the study (request 4). Therefore more information on those information requirements is needed to define an accurate hazard classification to the aquatic environment.

However, acute aquatic toxicity data are provided in the technical dossier that, in combination with fate data (degradability and bioaccumulation data), might warrant a classification for long-term aquatic hazard.

Regarding the fate data, in the technical dossier you have provided two ready biodegradability studies on the registered substance:

1) one key study ([redacted] 2003, reliability 1) according to OECD TG 301D with a reported degradation of 2% in 28 days;
2) one supporting study ([redacted] 1996, reliability 2) according to OECD TG301F with a reported degradation of 0-10% in 28 days.

These results indicate that the registered substance is not rapidly degradable based on the criteria set in the Annex I Section 4.1.2.9 of the CLP Regulation describing that a substance is considered to be not rapidly degradable unless the substance is demonstrated to be readily biodegradable (i.e. 60 % degradation) in a 28-day test for ready biodegradability.

Regarding the acute aquatic toxicity data, studies provided on aquatic invertebrates indicate that toxicity may occur in concentrations between 10 and 100 mg/L. In the technical dossier you have provided two short-term toxicity studies on aquatic invertebrates with the registered substance:

1) one key study ([redacted] 2004, reliability 2) according to OECD TG 202, 48h EC50 = 28.1 mg/L with pH adjustment;
2) one supporting study ([redacted] 1996, reliability 2) according to EEC Directive 79/831/EEC, Annex V, Part C, 48h EC 50 = 74.3 mg/L witout pH adjustment and 48h EC50 > 100 mg/L with pH adjustment.

Despite the observed toxicity between 10 and 100 mg/L in short-term toxicity to aquatic invertebrates and the substance being not rapidly degradable, you have not self-classified the substance for long-term aquatic hazards. Furthermore, ECHA observes that the dossier does not contain any justification for non-classification, but only the statement: "*conclusive but not sufficient for classification.*"

In the comments to the draft decision, you have provided further information on the algae study so that it can be considered valid (request 4. above) and agreed to carry out the long-term aquatic invertebrates study (request 5. above). In you comments you agree to reconsider the long-term aquatic hazard classification according to the CLP Regulation once the study on long-term toxicity to *Daphnia* (requested under point 5.) has been conducted on the registered substance.

ECHA notes that in your comments you have not justified the non-classification based on the available short-term *Daphnia* data and the substance being not rapidly degradable. In addition, ECHA notes that you have currently not provided an acceptable adaptation for long-term fish testing (requested under point 6.). However, ECHA acknowledges that the CSA, including classification, needs to be revised after information on long-term aquatic toxicity testing requested in this decision become available. In this regard, ECHA notes that you need to apply the classification according to the CLP regulation based on all available

information and refers you to the guidance given in Section 4.1.3.3. of ECHA's Guidance on the Application of the CLP Criteria (Version 5.0, July 2017).

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to classify and label the registered substance taking into account the information above. In the alternative, you are requested to provide the scientifically justified reasons why no such classification is given.

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 30 months from the date of adoption of the decision. In your comments to the draft decision, you requested that ECHA postpones the processing of this decision until data on the analogue substance DMEA (EC No 209-940-8 – CAS No 598-56-1) is available. You sought to justify this request by indicating that you intend to use this data, requested in a compliance check decision by ECHA, as source data for the endpoints sub-chronic toxicity in a revised read-across approach for the registered substance. The timeline for providing information set in the draft decision allows for the conduction of the sub-chronic toxicity, the screening study for reproductive/developmental toxicity and the pre-natal developmental toxicity studies with the registered substance is currently set to 30 months from the date of issuing the final decision. According to the deadline set in the CCH final decision on DMEA, the data from the sub-chronic toxicity study and from the pre-natal developmental toxicity study on the analogue substance DMEA is expected to be provided to ECHA by 30 August 2019, which is well within the 30-month timeline specified in the draft decision issued for EDIPA. ECHA outlines that the conduct of supporting vertebrate studies corresponding to information requirements listed in Annex VII or VIII and mentioned in the testing strategy presented in the comments to the draft decision may be initiated before ECHA issues its final decision. ECHA considers that this timeline allows for conducting the revised testing strategy described by the registrant in their comments and does not require any extension. Therefore, ECHA has not modified the deadline of 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 22 February 2017.

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) or the deadline.

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 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 requests in this decision, or to otherwise fulfil the information requirements 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 tests 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 tests 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 tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.