ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 23 August 2017

Addressee: [redacted]

Decision number: CCH-D-2114369268-37-01/F
Substance name: ETHYLDIMETHYLAMINE
EC number: 209-940-8
CAS number: 598-56-1
Registration number: [redacted]
Submission number: [redacted]
Submission date: 03.07.2012
Registered tonnage band: 1000+T

DECISION ON A COMPLIANCE CHECK

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

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

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

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

5. **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;**

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 are required to submit the requested information in an updated registration dossier by **31 May 2021** except for the information requested under point 1 for a sub-chronic toxicity study (90-day) which shall be submitted in an updated registration dossier by **30 August 2019**. You may only commence the extended one-generation reproductive toxicity study as requested under point 4 after **2 December 2019**, unless an indication to the contrary is communicated to you by ECHA before that date. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 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 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

0. Grouping of substances and read-across approach

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X 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 the endpoints *repeated dose toxicity (Annex IX, Section 8.6.2)*, *pre-natal developmental toxicity (Annex IX, Section 8.7.2. and Annex X, Section 8.6.2.) extended one-generation reproductive toxicity (Annex X, Section 8.6.3.)* and *long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)* adaptation arguments in the form of a grouping and read-across approach under Annex XI, Section 1.5. of the REACH Regulation. That means that you consider to achieve compliance with the REACH information requirements for the registered substance ethyldimethylamine (CAS no 598-56-1) using data of the structurally similar substances trimethylamine (CAS no 75-50-3), triethylamine (CAS no 121-44-8), and tributylamine (CAS no 102-82-9) (hereafter the 'source substances'). ECHA has considered first the scientific and regulatory validity of your read-across approach in general before assessing the individual endpoints (see sections 1-4 below)).

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "provided that the conditions set out in Annex XI are met". According to Annex XI, Section 1.5., there needs to be structural similarity among the substances within a group or category and furthermore, 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). Furthermore, Annex XI, Section 1.5., lists several additional requirements, including that adequate and reliable documentation of the applied method have to be provided.

Information provided

To support your read-across approach, you have provided the following studies for the endpoints repeated dose toxicity, pre-natal developmental toxicity, toxicity to reproduction and long-term toxicity to aquatic invertebrates:

- 28-week chronic inhalation toxicity study (equivalent to OECD 452) performed on *triethylamine* (CAS 121-44-8) at concentrations of 25 and 247 ppm, no histological effect was observed on the reproductive organs of male and female rats exposed 6 hr/day, 5 days/week to the highest concentration tested of 247 ppm (1022 mg/m3), reliability 2.

- Combined oral repeated dose and reproductive/developmental toxicity screening test (OECD 422) performed with *trimethylamine* (CAS 75-50-3) at dose levels of 8, 40, 200 mg/kg/day. The no observed effect level (NOEL) for reproductive and developmental toxicity was 200 mg/kg/day in male and female rats, and 200 mg/kg/day in pups, reliability 2.

- Pre-natal developmental toxicity study, oral (OECD 414) in rats performed with *tributylamine* (CAS 102-82-9) at dose levels of 0, 15, 45 and 135 mg/kg/day, the LOAEL for maternal toxicity was 135 mg/kg bw/day and the NOAEL was 45 mg/kg bw/day. The NOAEL for developmental toxicity was 135 mg/kg bw/day, reliability 1.

You have provided read-across documentation as a separate document.

You use the following arguments to support the prediction of properties of the registered substance from data for reference substance(s) within the group:

"This tertiary amines category is represented by R-N(R")-R'; the structure has a single and tertiary amino-group, where R is an aliphatic organic substituent. The nitrogen in an amine bears an unshared pair of electrons. The tendency to share these electrons underlies the chemical behaviour of amines as a group. Common features of the tertiary amines category include:

• A structure that contains only aliphatic organic substituents (including the aliphatic cyclohexyl group);
• A functional amine group that is tertiary in nature (all three hydrogen atoms are replaced by organic substituents);
• Elemental compositions of only carbon, hydrogen and nitrogen;
• A consistent incremental change across the category consisting of increasing number of carbon atoms; and
• Molecular weights of < 200 Daltons, classifying these tertiary amines as low molecular weight aliphatic amines.

The high electronegativity and lone pair electrons associated with the nitrogen underly the chemical behavior (basicity and nucleophilicity) of these tertiary aliphatic amines. The alkyl group may include a group that will not react with or substantially affect the properties of the amine function. The alkalinity is associated with the corrosivity of these compounds, one of the primary effects relevant for human health and a general feature of the compounds. Observed corrosive properties overwhelm the systemic toxicity of the tertiary amines in most cases, including acute toxicity; 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."

You propose that the source and registered substances have similar properties for the above-mentioned information requirements.

ECHA considers that this information is your read-across hypothesis.

ECHA's evaluation and conclusion

Your proposed adaptation argument is limited to stating that the similarity in structure and in physico-chemical properties between the source substances and target substance is a sufficient basis for predicting the properties of the substance.

Similarity in structure and physico-chemical properties is a prerequisite for applying the grouping and read-across approach, but ECHA does not accept in general or in this specific case that similarity in structure and physico-chemical properties per se is sufficient to enable the prediction of human health properties of a substance, since similarity in structure and physico-chemical properties does not always lead to predictable or similar human health properties. Further elements are needed[2], such as a well-founded hypothesis of (bio)transformation to common product(s), or information showing that the different compounds in the group have the same type of toxic effect(s). ECHA considers that the read-across approach should allow a prediction of human health properties that does not underestimate risks. In particular, there are the following deficiencies in your read-across approach:

i) You have not provided any systemic toxicity study involving repeated dosing with the registered substance and therefore comparison of systemic toxicity of the registered substance (target substance) with that of the source substances of the read-across cannot be made. You have claimed that "Observed corrosive properties overwhelm the systemic toxicity of the tertiary amines in most cases." However, you have not demonstrated that, in case non-corrosive concentrations are administered to test animals, it is impossible to observe systemic toxicity, independent of the corrosivity.

ii) You have not provided information that enables the comparison of the toxicokinetics of the registered substances and the source substances.

iii) You have not provided a basis for predicting the properties of the registered substance.

ECHA notes you provided comments on the draft decision regarding the read-across approach for the long-term toxicity to aquatic invertebrates, only. Based on this information, the long-term toxicity to aquatic invertebrates has been removed from the draft decision. These comments on the draft decision, do not address the issues highlighted above regarding the human health effects. For the reasons stated above, this grouping and read-across approach still does not provide a robust basis whereby the human health effects may be predicted from data for reference (source) substances within the group, and hence does not comply with the general rules of adaptation as set out in Annex XI, 1.5. of the REACH Regulation.

ECHA finally notes that there are specific considerations for the individual endpoints which also result in a failure to meet the requirement of Annex XI, 1.5, and these are set out under the endpoint concerned; more notably these considerations concern the Extended one-generation reproductive toxicity study.

[2] Please see for further information the Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of chemicals and ECHA's Read-Across Assessment Framework.

ECHA
EUROPEAN CHEMICALS AGENCY

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

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(e) and 13(4) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.

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.

In the technical dossier you have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422) with the analogue substance trimethylamine (CAS no 75-50-3) and a "chronic toxicity study" study according or similar to OECD TG 452 with the analogue substance triethylamine (CAS no 121-44-8) via the inhalation route. However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

Furthermore, the "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" does not provide the information required by Annex IX, Section 8.6.2., because exposure duration is less than 90 days. Indeed, Annex XI, section 1.5. third indent, provides that in all cases results should cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter.

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

In you comment to the draft decision, you have proposed that ECHA considers an extension of the deadline set for this study. ECHA has considered the reasoning and documentation you provided and revised the deadline as set out in the draft decision above.

ECHA has evaluated the most appropriate route of administration for the study. Since the registered substance is a liquid of very high vapour pressure (>10 kPa at 20°C) and human exposure by the inhalation route is reported in the registration, ECHA considers that the inhalation route is the most appropriate route of administration. 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.

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.

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

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

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records a prenatal developmental toxicity study (OECD TG 414) in rats with the analogue substance tri-n-butylamine (CAS no 102-82-9). However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected.

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

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

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) R.7a, chapter 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.

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

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

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

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(e) and 13(4) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.

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

The technical dossier contains information on a pre-natal developmental toxicity study in rats by the oral route using the analogue substance tri-n-butylamine (CAS no 102-82-9) as test material.

However, the technical dossier does not contain information on a pre-natal developmental toxicity study in a second species. Furthermore, the technical dossier does not contain an adaptation in accordance with column 2 of Annex X, Section 8.7.2. or with the general rules of Annex XI for this standard information requirement.

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

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) R.7a, chapter 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.

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

Notes for your consideration

You are reminded that before performing a pre-natal developmental toxicity study in a second species you must consider the specific adaptation possibilities of Annex X, Section 8.7.2., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.
The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 5.0, July 2016).
Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

a) The information provided

You have not provided any study record of an extended one-generation reproductive toxicity study in the dossier that would meet the information requirement of Annex X, Section 8.7.3.

Instead, you have provided the following information under IUCLID, Section 7.8.1:

- Key study: "*screening for reproductive / developmental toxicity*", oral (gavage), rat, (OECD TG 422; GLP not specified), analogue substance (EC no 200-875-0), [redacted] 2003, reliability 2
- Justification to omit "*two-generation reproductive toxicity study*":
  "*No reprotoxicity study (2-generation study) is available on dimethylethylamine. However, data on structural analogue substances, trimethylamine, triethylamine and tri-n-butylamine, indicate a low concern for reprotoxicity.*
  - In a 28-week chronic inhalation toxicity study (equivalent to OECD 452) performed on triethylamine at concentrations of 25 and 247 ppm, no histological effect was observed on the reproductive organs of male and female rats exposed 6 hr/day, 5 days/week to the highest concentration tested of 247 ppm (1022 mg/m3).
  - In a combined oral repeated dose and reproductive/developmental toxicity screening test (OECD 422) performed with trimethylamine at dose levels of 8, 40, 200 mg/kg/day. The no observed effect level (NOEL) for reproductive and developmental toxicity was 200 mg/kg/day in male and female rats, and 200 mg/kg/day in pups.

- In an oral developmental/teratogenicity study (OECD 414) in rats performed with tri-n-butylamine at dose levels of 0, 15, 45 and 135 mg/kg/day, the LOAEL for maternal toxicity was 135 mg/kg bw/day and the NOAEL was 45 mg/kg bw/day. The NOAEL for developmental toxicity was 135 mg/kg bw/day.
Therefore, the added value of the 2-generation study on dimethylethylamine would be very low compared to the available information on analogue substances.
Moreover, considering the DNEL of 6.1 mg/m3 (equivalent to an internal dose of 0.9 mg/kg bw/d) derived form the German MAK value, the marge of safety could be considered sufficient (> 100) when compared to the NOAE(C)L observed in these studies".

ECHA notes that you have provided justification to omit a two-generation reproductive toxicity study. However, a two-generation reproductive toxicity study is no longer a standard information requirement. It has been replaced by the requirement for an extended one-generation reproductive toxicity study (EU B.56./OECD TG 443).

In your justification you have referred to studies that were conducted with analogue substances. Hence, ECHA considers that you have sought to adapt the information requirement of Annex X, Section 8.7.3. according to Annex XI, Section 1.2., weight of evidence.

a) ECHA's evaluation and conclusion of the provided information

Criteria applied

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

A weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance at equivalent level as investigated in an extended one-generation reproductive toxicity study (EU B.56./OECD TG 443) as requested in this decision. ECHA considers that this study provides relevant information on two aspects, namely on sexual function and fertility in P1 and F1 generations (further referred to as 'sexual function and fertility') and on developmental toxicity observable peri- and postnatally in the F1 generation (further referred to as 'post-natal developmental toxicity'). Relevant elements for 'sexual function and fertility' are in particular functional fertility (mating behaviour, conception, pregnancy, parturition, and lactation) in the parental generation after sufficient pre-mating exposure and histopathological examinations of reproductive organs in both P and F1 generations. Relevant elements for 'post-natal developmental toxicity' are in particular peri- and post-natal investigations of the F1 generation up to adulthood.

ECHA considered whether the provided information fulfils the weight of evidence adaptation criteria according to Annex XI, 1.2. With this regard, ECHA notes that the provided information contains only limited information on sexual function and fertility, and no information on post-natal developmental toxicity.

Furthermore, ECHA notes that the studies you have provided under a weight of evidence adaptation, which have been specified above, have all been performed with analogue substances and not with the substance subject to this decision. However, as explained above in Appendix 1, section 0 of this decision, your read-across adaptation according to Annex XI, Section 1.5 is rejected.

Consequently, the information provided with those analogue substances are not acceptable as evidence, and therefore this information cannot be considered as adequate and reliable documentation within the meaning of the last sentence of Annex XI, 1.2 in order to fulfil the information requirement according to column 1 of section 8.7.3., Annex X.

Conclusion

Hence, ECHA can not accept the information included in your justification for the weight of evidence.

Accordingly, the information you provided to support your adaptation do not allow to assume/conclude that the substance does not have a particular dangerous (hazardous) property with respect to the information requirement for Annex X, Section 8.7.3.

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

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. Thus, an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3., is required. The following refers to the specifications of this required study.

b) The specifications for the study design

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

The sub-chronic toxicity study shall be conducted before the extended one-generation reproductive toxicity study and the results from that study shall be used, among to other relevant information, to decide on the study design of the extended one-generation reproductive toxicity study following ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 5.0, July 2016).The sub-chronic toxicity study may provide information on effects that is relevant for triggers (e.g. weight changes and histopathological observations of organs as indication(s) of one or more modes of action related to endocrine disruption which may meet the toxicity-trigger for extension of Cohort 1B or as evidence of specific mechanism/modes of action and/or neurotoxicity and/or immunotoxicity which may meet the particular concern criteria for developmental neurotoxicity and/or developmental immunotoxicity cohorts).

Premating exposure duration and dose-level setting

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

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 5.0, July 2016).

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

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

Species and route selection

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

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) R.7a, chapter 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.

c) Outcome

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

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

Currently, the extension of Cohort 1B and the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) are not requested. However, the sub-chronic toxicity study (90-day) requested in this decision (request 1) and/or any other relevant information may trigger changes in the study design. Therefore, the sub-chronic toxicity study (90-day) is to be conducted first and the study results submitted to ECHA in a dossier update by **30 August 2019**. If, on the basis of this update and/or other relevant information, a need for changes to the study design is identified, ECHA will inform you by **2 December 2019** (i.e. within three months after expiry of the 24-month deadline to provide the sub-chronic toxicity study (90-day)) of its intention to initiate a new decision making procedure under Articles 41, 50 and 51 of the REACH Regulation to address the design of the extended one-generation reproductive toxicity study. If you do not receive a communication from ECHA by **2 December 2019**, the request of the present decision for the extended one-generation reproductive toxicity study remains effective and you may commence the conduct of the study and the results will need to be submitted by the deadline given in this decision **31 May 2021**.

Notes for your consideration

When submitting the study results of the sub-chronic toxicity study (90-day) you are invited to also include in the registration update your considerations whether changes in the study design are needed (see also *ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.6 (version 6.0, July 2017*).

Furthermore, after having commenced the extended one-generation reproduction toxicity study in accordance with the ECHA decision, you may also expand this study to address a concern identified during the conduct of it and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the changes in the study design must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/ triggers must be documented.

5. 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 more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X 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: "*Experience gained in the frame of ecotoxicological testing demonstrates that fish is not the most sensitive species. Carrying out additional testing on fish would not contribute to improve the current knowledge of the substance and/or its associated risks when released to aquatic compartment.*"

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

ECHA notes that *ECHA's Guidance on information requirements and chemical safety assessment, Chapter R.7b, Section R.7.8.5.3.* (version 4.0, June 2017) clarifies that a risk from CSA is indicated if PEC is above respective PNEC, i.e. PEC/PNEC >1.

ECHA concludes that for several Exposure Scenarios/Environmental Release Categories risk to freshwater and marine water compartments is indicated. Therefore, the long-term toxicity study on fish is triggered.

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) are the preferred tests to cover the standard information requirement of Annex IX, Section 9.1.6.

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

Moreover, the FELS toxicity test is preferable for examining the potential toxic effects of substances which are expected to cause effects over a longer exposure period, or which require a longer exposure period to reach steady state (ECHA *Guidance Chapter R7b,* version 4.0, February 2017).
In your comments to the draft decision according to Article 50(1) of the REACH Regulation you provided the following information:

You indicated that you did not agree on testing long-term toxicity of DMEA in a Fish, early-life stage (FELS) toxicity test according to OECD TG 210. Instead, you propose to adapt the standard information requirement (Annex IX, Section 9.1.6. of the REACH Regulation) in accordance with Annex IX, Section 9.1.6. column 2, following a weight of evidence (WoE) approach for showing that fish is not the most sensitive aquatic species. Furthermore, you claim that long-term toxicity study results with fish would not reveal a greater hazard than already determined by the available data. You use this approach in order to justify the assessment factor (AF) of 10 instead of 50 for PNEC derivation and adapt the standard information requirement for long-term toxicity testing on fish (Annex IX, Section 9.1.6. of the REACH regulation).

The WoE approach you propose takes into account:

1) A relative species sensitivity, indicating that the factor between the acute toxicity of fish and daphnids or algae is about 10 for DMEA with fish being less sensitive.

2) An assessment of acute toxicity to fish, indicating that the observed toxicity of DMEA is triggered by an alkaline pH at high test item concentrations when exposed to a not neutralized test solution. However, DMEA is acutely not harmful to aquatic fish when exposed to a pH-adjusted test solution: no mortality has been observed at 100 mg/L (nominal concentration).

3) An acute to chronic ratio-approach (ACR), indicating that NOECs are expected to be greater than 1 mg/L and thus long-term effects are not to be expected.

4) Risk Characterisation Ratio (PEC/PNEC), indicating no unacceptable risk for the aquatic environment as RCRs<1.

5) Data available for the source substance (trimethylamine) conducted similarly to OECD 210.

6) Animal welfare considerations.

ECHA acknowledges that you have provided reasoning and documentation for the WoE approach. However, ECHA notes the following issues concerning your proposed approach for fish:

1) ECHA observes that only the QSAR results for short-term aquatic toxicity indicate significant difference in species sensitivity. At the same time the experimental EC50 values for the registered substance were between 24.2 – 38.29 mg/L across all the three trophic levels for the non-neutralized test solution, thus, based on all evidence available, no difference in species sensitivity can be noted. Furthermore, as acknowledged by you in your comments, QSAR predictions for the chronic toxicity have high level of uncertainty and thus cannot be considered reliable.
In addition, the QSAR run by you predicts ChV < 1mg/L for the invertebrates. If considered reliable, this result may trigger the need for classification in accordance with CLP.

2) The evidence available suggests that alkaline pH originating from the chemical nature of the registered substance appears to affect toxicity of the non-neutralized test solution and exposure to a pH-adjusted test solution leads to no mortality at 100 mg/L level. However, results for pH-adjusted test solutions are only available for the fish. Therefore, this result cannot be compared with other trophic levels and is thus insufficient for the determination of the relative species sensitivity.

3) ECHA considers that the aquatic PNEC for the registered substance has been derived incorrectly using an AF of 10, while no difference in species sensitivity can be determined for the registered substance. According to the *ECHA Guidance on information requirements and chemical safety assessment, Table R10.-4*, the assessment factor to be used when only two long-term toxicity studies are available is 50. This leads to RCRs>1, thus indicating risk for the aquatic environment and the need to investigate further the effects on aquatic organisms (Annex IX, Section 9.1.6. Column 2 of the REACH Regulation).

4) ECHA also notes that being a theoretical model, an acute to chronic ratio approach (ACR) cannot itself provide sufficient information on potential long-term toxicity effects of a specific substance. You have not demonstrated that, considering their uncertainties or shortcomings, other pieces of evidence provided would address this concern.

5) In addition, you provided the results of the long-term toxicity study for a source substance (trimethylamine) conducted similarly to OECD 210. However, you have not provided a robust study summary and from the information available it seems that the only long-term toxicity study results reported were 60d LOECs, whereas a NOEC should have been provided because that is needed for the risk assessment (as required under Annex XI, Section 1.5, last paragraph, third indent). Thus, this study does not provide sufficient information for use in a WoE or read-across approach based on the current information.

In conclusion, you have not demonstrated that the proposed pieces of evidence, either alone or together, leads to the assumption/conclusion that a substance has or has not a particular dangerous property. Based on the discussion above, these pieces of evidence, either alone or together, do not either allow concluding that fish is the less sensitive species.

ECHA concludes that due to the above reasons the proposed adaptation is not acceptable. Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Fish, early-life stage (FELS) toxicity test (test method: OECD TG 210).

Notes for your consideration

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

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, February 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.

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017), Chapter R.7a, section R.7.6.2.3.2, Stage 4 (iv), "*In certain cases, testing of neutral salts of alkaline or acidic substances may be appropriate and allows investigation of intrinsic properties at adequate dose levels*".

Due to the volatility of the substance 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 and for calculation and expression of the result of the test(s).

Deadline to submit the requested information in this decision

In the draft decision communicated to you the time indicated to provide all the requested information was 42 months from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of the timeline of the 90-days toxicity study to 24 months. You sought to justify this request by providing adequate reasoning (related e.g. to the recovery period and analytical method) and documentation from your CRO stating that they are not able to meet the deadline of 12 months. Furthermore, you have explained that the CRO will use the study results to re-evaluate and validate their read-across possibilities. ECHA notes, your submitted information to prolong the deadline are acceptable. Therefore, ECHA has granted the request and set the deadline of the 90-days study to 24 months. As a result of this change for the 90-day toxicity study, the overall decision's deadline has been changed from 42 months to 45 months.

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 2 November 2016.

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

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

ECHA took into account your comments and amended the request(s).

Note the draft decision request of long-term toxicity to aquatic invertebrates has been removed from the draft decision. Your submitted comments on the revised read-across approach for this endpoint is considered to fulfil this information requirement.

On 8 June 2017 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals for amendment of the draft decision within 30 days of the receipt of the notification.

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.