EUROPEAN CHEMICALS AGENCY

Helsinki, 23 November 2018

Addressee: [redacted]

Decision number: CCH-D-2114449807-36-01/F
Substance name: N,N-DIMETHYLISOPROPYLAMINE
EC number: 213-635-5
CAS number: 996-35-0
Registration number: [redacted]
Submission number: [redacted]
Submission date: 1 June 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;**

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 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.

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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.

Appendix 1: Reasons

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 according to Annex XI, 1.5. of the REACH Regulation. ECHA has assessed first the scientific and regulatory validity of your Grouping and read-across approach in general before 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 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.

[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.

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.

A. 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, N,N-dimethylisopropylamine (EC 213-635-5) (CAS No 996-35-0) as target substance.

- N,N-dimethylmethanamine (TMA), CAS No 75-50-3
- N,N-dimethylethylamine (DMEA), CAS No 598-56-1
- N,N-dimethylpropan-1-amine (DMPA), CAS No 926-63-6
- 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).

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

ECHA considers that your read-across hypothesis is based upon the claim that 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. However, there is insufficient information to support these claims in your read-across hypothesis in the registration dossier.

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. While ECHA agrees that the target and source substances would cause similar *local effects* due to their irritant and/or corrosive properties, it does however not agree that the available evidence is sufficient to conclude on the similarity between the target and source substances regarding *systemic 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. ECHA notes 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 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.

In your comments to the draft decision, you have presented a revised adaptation in the form of a "*Tertiary Amines Category*" including three substances: N,N-dimethylisopropylamine (DMIPA), i.e. the substance subject to this decision, ethyldiisoprpylamine (EDIPA - CAS No 7087-68-5 – EC No 230-392-0) 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 substance "*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 (the registered substance) and EDIPA and to compare the outcome of these studies with the results from similar studies conducted with the source substance DMEA. You also suggested that you would use information from ongoing or upcoming pre-natal developmental toxicity studies on the analogue substances DMEA and EDIPA "*if comparable toxicity profiles are obtained*".

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 DMPA 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 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 currently presented cannot be accepted.

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

C. 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 or ecotoxicological 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.

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

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.

"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. However, ECHA notes that no data from a pre-natal developmental toxicity study is currently available and included in the registration dossier of DMIPA.

From the information provided in the comments to the draft decision, ECHA understands that you do not intend to conduct a pre-natal developmental toxicity study with DMIPA. The table included on page 4 of your comments suggests that your intention is to use information from an ongoing OECD 414 study conducted with the analogue substance DMEA and results from an upcoming OECD 414 study with EDIPA as source data to fulfil this information requirement for DMIPA and thereby adapt the information requirement for the screening study on reproductive/developmental toxicity.

ECHA points out that in order to support such an adaptation based on the provisions of Annex VIII, 8.7.1 column 2 your dossier should either contain a pre-natal developmental toxicity study conducted with the registered substance to fulfil the information requirement of Annex IX, Section 8.7.2 or include a read-across approach for the information requirement of Annex IX, Section 8.7.2 meeting the conditions for adaptation presented in Annex XI, Section 1.5. This is currently not the case, neither for the approach assessed in this decision nor for the approach outlined in your comments as outlined in more details in ECHA's response to your comments in "ECHA analysis of the grouping and read-across approach" and in section 3 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: 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 consideration

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).

You should also carefully consider the order of testing of the requested screening (OECD TG 421/422) and the developmental toxicity studies (OECD TG 414) to ensure that unnecessary animal testing is avoided, paying particular attention to the endpoint 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. Takashima, 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. Kinney, 1990, weight of evidence, 14-day repeated dose toxicity study conducted in rats via the inhalation route using N,N-dimethylmethanamine (TMA);
4. Rotenberg and Mashbits, 1967, weight of evidence, 7-month repeated dose toxicity study conducted in rats via the inhalation route using N,N-dimethylmethanamine (TMA);
5. [redacted], 1979, weight of evidence, 8-day repeated dose toxicity study conducted in rats via the inhalation route using the registered substance;
6. [redacted] 1979, weight of evidence, 7-day repeated dose toxicity study conducted in mice via the inhalation route using the registered substance;

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

3. 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 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.

4. Rotenberg, 1967: 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. The insufficient level of reporting prevents assessing the adequacy of the study design. Even though systemic toxicity has been observed in the liver, spleen and kidney, no information on the exact method of administration and on the composition and purity of the test material is provided. Only two test doses were used and no information on the sex of the animals dosed in this study is provided. In the light of this limited reporting, ECHA considers that this information is not sufficient on its own to fulfil the information requirement of Annex IX, Section 8.6.2. for a sub-chronic toxicity study (90 day). However in the context of a weight of evidence approach, ECHA considers that this study provides relevant information on the toxicological properties of TMA after repeated exposure via inhalation route.

5. and 6.: [redacted] 1979: both of these studies have been flagged as part of a weight of evidence approach for the repeated dose toxicity of the registered substance after inhalation exposure. Even though these studies have been conducted with the registered substance and provide information on the absence of death of animals after 8 and 7 exposures, respectively, the limited information reported on the design of these studies prevent from concluding on the reliability of this data and its adequacy and relevance in the context of a weight of evidence approach to fulfil the information requirement of Annex IX, Section 8.6.2. for a sub-chronic toxicity study (90 day). This conclusion is in line with your assessment of the reliability of these studies to which you assigned a Klimisch score of 4 – not assignable.

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 very high vapour pressure (189.9 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 quantitative 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 "*Tertiary 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 DMIPA (the registered substance) and EDIPA (CAS No 7087-68-5 – EC No 230-392-0) 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 (see our 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 provided, ECHA concludes that the proposed adaptation cannot be accepted as currently presented. 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) flagged as key study and a study record for a study investigating the *in vivo* developmental toxicity potential of the analogue substance N,N-dimethylmethanamine (TMA) (EC) (Guest and Varma, 1991) flagged as supporting study.

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

ECHA further points out that both studies have been conducted with different analogue substances in different species and via different routes of administration: the study by [redacted] was conducted using TBA via the oral route in rats whereas the study by Guest and Varma was performed using TMA via the intraperitoneal route in mice. These fundamental differences in the study designs and particularly the use of the IP route in a non-guideline study prevent any comparison of the outcome of these studies and cannot serve, without further scientific explanation, as a basis for predicting the properties under consideration for the substances included in this read-across approach.

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 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.

You have not provided endpoint-specific comments for this request, however as a footnote from Table 4 in your comments you have indicated that for pre-natal developmental toxicity, "*read-across to be applied if comparable toxicity profiles are obtained from the 2 developmental studies performed with DMEA (lowest MW= 87.16) and EDIPA (highest MW=129)*".

ECHA understands from this information that you intend to fulfil this information requirement by using information from ongoing or upcoming pre-natal developmental toxicity studies on the analogue substances DMEA and EDIPA "*if comparable toxicity profiles are obtained*". You suggest using interpolation to predict effects for DMIPA based on the information obtained from DMEA and EDIPA which you present as having the lowest and highest molecular weights for these three substances, respectively. However, ECHA points out that you did not explain why molecular weight is an appropriate parameter in this

proposed category to interpolatate effects observed in pre-natal developmental toxicity studies. 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 emphasises that comparable results obtained in studies with DMEA and EDIPA would indicate that these substances do have a similar toxicity profile for this endpoint. However, in the absence of further relevant supporting information, this would not constitute evidence of similarity between the properties of these analogue substances and DMIPA. In this context, ECHA stresses that a screening study for reproductive/developmental toxicity with the registered substance may provide valuable information for such a read-across approach. ECHA also observes that you have neither provided considerations nor outlined your plans on how to comply with the REACH Regulation in case the read-across hypothesis is not confirmed by the data proposed to be generated.

Based on the information provided, ECHA concludes that the proposed adaptation cannot be accepted as currently presented. 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: Pre-natal developmental toxicity study (test method: OECD TG 414) in a first species (rat or rabbit) by the oral route.

Deadline to submit the requested information in this decision

In your comments on the draft decision, you ask ECHA to postpone the processing of this decision until data on the analogue substance DMEA 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 and pre-natal developmental toxicity in a revised read-across approach for the registered substance.

The timeline for providing information set in the draft decision allows for the conduct of the sub-chronic toxicity and the pre-natal developmental toxicity studies and is currently set to 30 months from the date of issuing the decision. According to the deadline set in the compliance check 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 DMIPA, the substance subject to the current decision. The results obtained with DMEA may therefore be considered in the refinement of the testing strategy to comply with the REACH information requirements. In addition, ECHA outlines that supporting vertebrate studies corresponding to information requirements listed in Annex VII or VIII and mentioned in your testing strategy as presented in the comments

to the draft decision may already be initiated before ECHA issues its decision. This may provide you with the information to assess your strategy and change it to achieve compliance, if needed. ECHA considers that the timeline of 30 months allows for your testing strategy and also for changes if the results obtained are not as expected, and does not require any extension or postponement. 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).

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

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

Appendix 3: Further information, observations and technical guidance

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

2. Failure to comply with the 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 à 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.