Helsinki, 22 November 2018

Addressee: [redacted]

Decision number: CCH-D-2114449808-34-01/F
Substance name: N,N-BIS[3-(DIMETHYLAMINO)PROPYL]-N',N'-DIMETHYLPROPANE-1,3-DIAMINE
EC number: 251-459-0
CAS number: 33329-35-0
Registration number: [redacted]
Submission number: [redacted]
Submission date: 16 September 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. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. / OECD TG 471) with the registered substance;**

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

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

4. **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;**

5. **Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: Fish, acute toxicity test, OECD TG 203) with the registered substance;**

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

7. **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 have to submit the requested information in an updated registration dossier by ***31 May 2021***. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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

Appeal

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

Authorised[1] by Ofelia Bercaru, Head of Unit, Evaluation E3

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

Appendix 1: Reasons

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

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.

An "*In vitro* gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. 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.

According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA.

Other tests may be used if the conditions of Annex XI are met. More specifically, Section 1.1.2 of Annex XI provides that existing data on human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) may be used if the following conditions are met:

(1) Adequacy for the purpose of classification and labelling and/or risk assessment;
(2) Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) adequate and reliable documentation of the study is provided.

According to paragraph 13 of the current OECD TG 471 test guideline (updated 1997) at least five strains of bacteria should be used: S. typhimurium TA1535; TA1537 or TA97a or TA97; TA98; TA100; S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). This includes four strains of S. typhimurium (TA1535; TA1537 or TA97a or TA97; TA98; and TA100) that have been shown to be reliable and reproducibly responsive between laboratories. These four S. typhimurium strains have GC base pairs at the primary reversion site and it is known that they may not detect certain oxidising mutagens, cross-linking agents and hydrazines. Such substances may be detected by E.coli WP2 strains or S. typhimurium TA102 which have an AT base pair at the primary reversion site.

You have provided a test from the year 1987 ([redacted]) according to OECD TG 471 and GLP with an assigned reliability score of 2. The test used four different strains of S. typhimurium TA 1535, TA 1537, TA 98 and TA 100 and it did not include tests with strains S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). However, since the test was conducted, significant changes have been made to OECD TG guideline 471 so that additionally testing with S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) is now required. Therefore, the provided study does not meet the current guidelines, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation.

ECHA concludes that a test using *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S.*

typhimurium TA102 has not been submitted and that the test using one of these is required to conclude on *in vitro* gene mutation in bacteria.

In your comments to the draft decision you indicated your intention to repeat the requested bacterial reverse mutation test.

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: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102.

2. 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.

The dossier contains a read-across justification document which is attached to the endpoint study record for repeated dose toxicity (28-day study) ([redacted], 2012). In this document it is mentioned that a reproductive toxicity screening study is ongoing with the registered substance. However, 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.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement. In the waiver included in section 7.8.1. of the IUCLID dossier and in section 5.9.1.1 of the Chemical Safety Report, you refer to the findings observed in a 28-day repeated dose toxicity study conducted with the registered substance, outlining that this study "*revealed effects primarily associated with the corrosive effects of the substance*". You concluded on the basis of this data that "*The results of these studies strongly indicate that the corrosive effects of Polycat9 are the cause of all observed effects. Although a NOAEL was derived, it's relevance is questionable. Only animals in the high-dose group showed significant effects, and these are consistent with the animals being dosed with a corrosive. Thus, it is proposed to focus on a qualitative human health assessment, wherein exposure to the substance is to be avoided. Any exposure to the substance will elicit immediate irritating effects, and lead to self rremoval. The chance of chronic exposure to this substance is extremely unlikely. For this reason, and in consideration of animal welfare concerns, further vertebrate studies are not warranted*".

ECHA understands that you intend to claim that the properties of the registered substance are primarily associated with effects caused by its corrosive properties. On this basis, you propose to address these hazards in a qualitative risk assessment rather than by conducting further testing for the endpoint under consideration.

ECHA points out that the identification of corrosive properties and the development of a qualitative risk assessment do not constitute valid reasons for waiving the information requirement of Annex VIII, section 8.7.1 for a screening study for reproductive/developmental toxicity for hazard identification purposes.

Further, there is no adaptation provided in light of the corrosive property of the substance. ECHA also stresses that you have not demonstrated that testing the registered substance is technically not feasible under Section 2 of Annex XI of the REACH Regulation or would cause unnecessary animal suffering. To the contrary, increases in the relative weights of kidneys, ovaries, uterus in females of the high dose group have been reported in the 28-day repeated dose toxicity study, together with increased relative weight of the pituitary gland in treated satellite females and decreased weight of epididymides in treated satellite males. Based on the information provided, testing of the registered substance at a dose that does not cause corrosivity appears feasible and justified and these observations suggest that the registered substance may cause systemic toxicity which may not be secondary to its corrosive properties and which warrants further investigations on the reproductive toxicity of the substance.

Furthermore, ECHA considers that a 28-day repeated dose toxicity study performed with the registered substance cannot be used, on its own, to fulfil the information requirement of Annex VIII, Section 8.7.1., because it does not cover key parameters of a screening study for developmental/reproductive toxicity, with examinations of effects of a test substance on male and female reproductive performance such as gonadal function, mating behaviour, conception, development of the conceptus and parturition.

Therefore, ECHA concludes that you have neither established that testing with the registered substance is technically unfeasible based on the corrosive properties of the substance nor that testing the registered substance for reproductive toxicity is scientifically unjustified under the REACH Regulation . Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test methods OECD TG 421 or 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.

ECHA draws your attention to the recommendations of the ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6.2.3.2, Stage 4.1 (iv) (version 6.0, July 2017) indicating that "*It is to be noted that corrosive or highly irritating substances should be tested preferentially via the oral route, however it must be noted that in vivo testing with corrosive substances at concentration/dose levels causing corrosivity must be avoided (see REACH Annex VII-X preamble). The vehicle should be*

chosen to minimise gastrointestinal irritation. For some substances dietary administration may allow adequate dosing without irritation compared with oral gavage dosing. 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".

In your comments to the draft decision you expressed your intentions to fulfil this information requirement by using information from an existing OECD 422 screening study conducted with the proposed analogue substance N -[3-(Dimethylamino)Propyl]-N,N',N'-Trimethylpropane-1,3-Diamine (EC 223-362-3, CAS 3855-32-1). You have provided a preliminary read-across justification document and a summary of a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test performed with the above mentioned analogue substance (thereafter Polycat 77). According to your read-across justification, the read-across hypothesis is based on structural similarity between the analogue substance and the registered substance and the claim that the toxicological properties of these substances are driven by their irritant or corrosive properties.

Whilst the documentation provided alongside the comments is presented as preliminary, ECHA has reviewed it and concludes that as currently presented it does not meet the requirements of Annex XI, Section 1.5 of the REACH Regulation for the reasons detailed below.

In the read-across justification document submitted alongside your comments, you indicate that "*the physical-chemical properties compare well with structure, as an increase in side groups leads to an increase in melting point, boiling point and partition coefficient, and a decrease in vapour pressure and water solubility*" and that the "*catalytic activity of tertiary amines depends on their structure and alkalinity*". These variations in the physico-chemical properties of the source and target substance and in their catalytic activities suggest that the structural differences between these substances may affect their properties. You have not provided considerations on the impact of these structural differences on the toxicological properties under consideration. Instead, one key element in your proposed read-across approach is that the "*toxicological properties, which are dominated by irritation and corrosion leading to tissue destruction - a feature of the category – as well as narcotic effects*". You also indicate in the read-across justification that "*the target substance exhibits corrosivity that is more severe than the source substance, and therefore that maternal toxicity is likely to be again the driver*".

Based on the information provided in the attachments to the comments and the data reported in the dossier, ECHA observes that systemic toxicity has been detected in the form of vacuolation in multiple tissues. Whilst some of these effects may be attributed to the irritant or corrosive properties of the substance, others cannot be associated with these properties. Specifically, an array of microscopic effects affecting the reproductive organs, the central nervous system tissues are reported in the adult animals from the mid and high doses in the screening study for reproductive and developmental toxicity on Polycat 77. These effects were persisting and considered more severe in the high dose recovery group. These observations were concluded to be treatment related and the low dose of 50 mg/kg/d was set as NOEL.

In view of these differences, ECHA therefore considers that the information provided in the dossier contradicts your read-across hypothesis that the properties of the source and registered substances are mainly driven by irritation and corrosion properties.

In the study conducted with Polycat 77, ECHA also observes that multiple findings were reported for the dams and the offspring in the high dose group: pregnancy index of 80% vs mating index of 100%, decreased proportion of males at post-natal day (PND) 1 not observed at PND 4 associated with "*possible litter mortality*". The level of details provided in the summary of the study does not allow for an independent assessment of these findings, however ECHA notes that no robust explanation for considering these effects as not treatment related has been included in the summary. You conclude in the read-across justification document that "*in all cases no reproductive and developmental toxicity was observed*" with the substances considered in the read-across approach. The above-mentioned study is the only source study reported in your documentation of the adaptation. You did not address the relevance and the impact of the above-mentioned findings on the prediction of the reproductive and developmental toxicity properties of the target substance.

With regard to the prediction of the properties under consideration of the target substance, you state in your read-across justification document that "a conservative, worst-case NOAEL of 100 mg could adopted" for reproductive and developmental toxicity. You report that this NOAEL is based on "*NOELs available for other tertiary amines, as taken from the REACH publicly disseminated data*". You conclude that "*the evidence from reproductive/development studies on other tertiary amines strongly suggest that similarly testing the target substance would lead to similar results: maternal toxicity due to corrosive effects of oral/dermal dosing and a lack of reproductive/developmental toxicity even in high dose groups where there is clear indication of animal distress*" and that "*it is therefore highly doubtful that performing an additional reproductive/developmental study on the target substance would demonstrate effects not seen in the source substance or other tertiary amines*".

Only two substances are described in the justification document, no category definition and justification has been developed. Therefore, based on the information ECHA is of the opinion that this read-across is an analogue approach and cannot be considered as a category approach. ECHA points out that you have not provided any information neither on the identity of the other tertiary amines referred to in your justification nor on the nature of the experimental data from which the prediction is made. You have also not established how and why the information generated from these "other tertiary amines" constitute relevant information to predict properties of the registered substance by means of read-across in accordance with the requirements of Annex XI, section 1.5 of the REACH Regulation. There is no data on toxiciokinetics, which demonstrate which substances are systemically present after administration of potential source and target substances. Furthermore, ECHA stresses that the information disseminated on its website cannot be used directly or referred to for regulatory purposes by third parties without the permission of the data owners. Further, no details on the considerations leading to the identification of 100 mg/kg/d as a conservative NOAEL are provided. Finally, there is currently no information on reproductive/developmental toxicity available for the registered substance which can be used to verify predictions based on information obtained with other tertiary amines.

ECHA notes that all of the shortcomings addressed above need to be addressed, if you intend to continue with your read–across approach. If this is the case, ECHA will assess in the follow-up process according to Art 42 of the REACH Regulation whether the provisions of Annex XI, Section 1.5 are met. In this regard ECHA points out that read-across approaches are assessed using the Read-Across Assessment Framework (https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a).

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Reproductive/developmental toxicity screening test (test method: OECD TG 421) *or* Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

Notes for your considerations

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

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."

3. Sub-chronic toxicity study (90-day), oral 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 provided information from a 28-day repeated dose toxicity study conducted in rats via the oral route using the registered substance ([redacted] 2012). You have not provided any study record of a sub-chronic toxicity study (90 day) in the dossier that would meet the information requirement of Annex IX, Section 8.6.2.

You have provided possible adaptations that are similar to those provided for the screening for reproductive/developmental toxicity endpoint. These adaptations must be rejected for the same reasons as presented in Section 2 above. ECHA further points out that a NOAEL of 200 mg/kg/d was identified in the 28-day repeated dose toxicity study. No local toxicity in the gastro-intestinal tract was reported at this dose in the technical dossier. This indicates that testing the registered substance at doses which do not cause local effects is possible.

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. The substance is a corrosive liquid. Based on the information reported in the dossier, the industrial uses include industrial spraying (PROC 7) and the professional uses include non-industrial spraying (PROC 11). Therefore exposure of the respiratory tract and local respiratory effects cannot be excluded. Local respiratory effects have been addressed by a qualitative risk assessment; therefore ECHA considers that further investigations of the

systemic toxicity of the substance subject to this decision should be conducted via the oral route. The recommendations of the ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6.2.3.2, Stage 4.1 (iv) (version 6.0, July 2017) on testing irritant or corrosive substances referred to in section 2 above also apply to this endpoint.

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

ECHA understands from the information provided in your comments to the draft decision that you intend to fulfil this information requirement by using information from an ongoing or upcoming sub-chronic (90-day) repeated dose toxicity study on the analogue substance N -[3-(Dimethylamino)Propyl]-N,N',N'-Trimethylpropane-1,3-Diamine (EC 223-362-3, CAS 3855-32-1).

ECHA points out that the source data mentioned in your comments is not available yet. ECHA also observes that you have not provided any read-across hypothesis and justification for this adaptation fulfilling the requirements of Annex XI, Section 1.5 of the REACH Regulation.
The proposed adaptation, as currently described in your comments is not acceptable. If you intend to continue with your read–across approach ECHA will assess in the follow-up process according to Art 42 of the REACH Regulation whether the provisions of Annex XI, Section 1.5 are met. In this regard ECHA points out that read-across approaches are assessed using the Read-Across Assessment Framework (https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a).

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

4. 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 not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2.

You have provided possible adaptations that are similar to those provided for the screening for reproductive/developmental toxicity endpoint. These adaptations must be rejected for the same reasons as presented in Section 2 above. Furthermore, ECHA points out that a 28-day repeated dose toxicity study performed with the registered substance cannot be used,

on its own, to fulfil the information requirement of Annex IX, Section 8.7.2., because it does not cover key parameters of a pre-natal developmental toxicity study, like development of the conceptus, examinations of foetuses for skeletal and visceral alterations.

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. The recommendations of the ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6.2.3.2, Stage 4.1 (iv) (version 6.0, July 2017) on testing irritant or corrosive substances referred to in section 2 above also apply to this endpoint.

ECHA understands from the information provided in your comments to the draft decision that you intend to fulfil this information requirement by using information from an ongoing or upcoming pre-natal developmental toxicity study on the analogue substance N -[3-(Dimethylamino)Propyl]-N,N',N'-Trimethylpropane-1,3-Diamine (EC 223-362-3, CAS 3855-32-1).

ECHA points out that the source data mentioned in your comments is not available yet. ECHA also observes that you have not provided any read-across hypothesis and justification for this adaptation fulfilling the requirements of Annex XI, Section 1.5 of the REACH Regulation.

The proposed adaptation, as currently described in your comments, is not acceptable. If you intend to continue with your read–across approach ECHA will assess in the follow-up process according to Art 42 of the REACH Regulation whether the provisions of Annex XI, Section 1.5 are met. In this regard ECHA points out that read-across approaches are assessed using the Read-Across Assessment Framework (https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a).

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.

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

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.

"Short-term toxicity testing on fish" is a standard information requirement as laid down in Annex VIII, Section 9.1.3. 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 provided the following two study records to fulfill the information requirements for this endpoint:

1) key study conducted with the analogue substance N-[3-(dimethylamino)propyl]-N,N',N'-trimethylpropane-1,3-diamine (EC No 223-362-3, CAS No 3855-32-1): [redacted] (1998), report number [redacted], Title: *"N;N;N';N'';N''-Pentamethyldipropylentriamin: Acute toxicity study on the zebra fish (Brachydanio rerio HAM. and BUCH. in a static system (96 hours)"*, GLP compliance: yes, test method: according to OECD Guideline 203 (Fish, Acute Toxicity Test).
2) supporting study with the registered substance: report number [redacted] ([redacted], Title: *"The degree of accumulation test in carp: 3,3',3'-tris (dimethylamino) tripropylamine"*, GLP compliance: NA, test method: according to JIS K-0102.

ECHA has evaluated the information provided on this endpoint in the technical dossier and considers that it does not meet the information requirement, as explained in the following. By submitting a key study on the analogue substance, you have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by read-across information from Fish, Acute Toxicity Test according to OECD Guideline 203 conducted with the analogue substance N-[3-(dimethylamino)propyl]-N,N',N'-trimethylpropane-1,3-diamine (EC No 223-362-3, CAS No 3855-32-1).

In order to justify this read-across approach you have attached a read-across justification report to the endpoint study record for the study. You describe that *"The substances are structurally similar aliphatic tertiary amines. Structurally, CAS 33329-35-0 differs only in the presence of an additional (dimethylamino)propyl group linked to the central nitrogen"* and that *"Both substances are highly water-soluble and have similar partition coefficients. Both substances have the same physical state (liquid) with comparable surface tensions, boiling points and melting points. Given this close similarity, behaviour in the environment driven by physicochemical properties (such as organic carbon binding, fugacity, partitioning and bioavailability) is expected to be highly similar. (...)"*

Regarding ecotoxicity of the substances you state: *"non-target environmental organism toxicity data indicates broadly the same ecotoxicology profiles for each substance. In all cases equivalent endpoints for core aquatic toxicity studies are within one order of magnitude. For example in a Daphnia acute toxicity study the acute EC50 is 34.4 mg/L for CAS 3855-32-1 and 48 mg/L for CAS 33329-35-0.*

You further provided the following endpoint-specific information: *"Acute endpoints for fish are more difficult to compare directly, as the testing of each substance was conducted with different species and different test durations. A 96-hour test in zebra fish was conducted forCAS3855-32-1, while a 48-hour test in Medaka was conducted for CAS 33329-35-0. Nevertheless, the derived endpoint values were within the expected range of interspecies variability at LC50 = 92.5 mg/L and TLm = 430 mg/L, respectively."*

Based on these you conclude that "*Given the above it is considered that the environmental behaviour and ecotoxicology profiles for CAS 3855-32-1 and CAS 33329-35-0 are sufficiently equivalent for the purposes of read across*".

ECHA has evaluated the information and documentation provided in the registration dossier in light of the requirements of Annex XI, Section 1.5 of the REACH Regulation and concludes that the requirements of Annex XI, Section 1.5 are not met for the following reasons.

Impact of the structural differences on the prediction of properties

According to the provisions of Annex XI, section 1.5 of the REACH Regulation, structural similarity is a prerequisite for applying grouping and read-across approaches. However, structurally similar substances still exhibit differences in their chemical structures. The potential impact of these structural differences on the properties of the substances needs to be accounted for in the read-across hypothesis and justification in order to establish that the substances are likely to have similar fate and ecotoxicological properties, as required by the provisions of Annex XI, section 1.5, and in turn that the fate and ecotoxicological properties of the target substance can be predicted from data on the source substance.

You have indicated in your read-across justification that the source and target substances are structurally similar in that they both are aliphatic tertiary amines. However, ECHA observes that despite this structural similarity, the source and target substances exhibit significant structural differences. Specifically, and as you pointed out in your read-across justification, the substances differ by "*the presence of an additional (dimethylamino)propyl group linked to the central nitrogen*" in the source substance.

Your read-across hypothesis for this endpoint is based on structural similarity; on similarities in physico-chemical, fate and ecotoxicological properties; on similar EC50 values ("*within one order of magnitude*") observed in a *Daphnia* acute toxicity study performed with the source and target substances and on similar endpoint values ("*within the expected range of interspecies variability*") observed in fish acute toxicity studies performed with the source and target substances on different species and with different test durations. ECHA points out that you have not provided in your read-across hypothesis and justification, an assessment supported by scientific justifications of the impact of the identified structural differences between the source and the target substances on the properties of these substances. In the absence of this information ECHA concludes that you have not provided an adequate basis for predicting the properties of the registered substance from the source substances as required by the provisions of Annex XI, section 1.5 of the REACH Regulation.

Missing supporting evidence

According to the provisions of Annex XI, Section 1.5 of the REACH Regulation, the properties of substances used in read-across approaches must be likely to be similar or follow a regular pattern. ECHA notes that there is insufficient information supporting your read-across hypothesis and claim of similarity in the properties of the source and the target substances in the registration dossier. You claim that the substances have similar EC50 values ("*within one order of magnitude*") in a *Daphnia* acute toxicity study performed with the source and target substances and on similar endpoint values ("*within the expected range of interspecies variability*") observed in fish acute toxicity studies performed with the

source and target substances on different species and with different test durations.

ECHA points out that the results of the short-term fish toxicity tests conducted with the target and source substances cannot be compared, because, as you indicated, different fish species and different durations exposures have been used. In addition, ECHA notes that the comparison of toxicity based on *Daphnia* acute toxicity studies conducted with the target and source substances cannot be established, because the validity of the Daphnia study for the source substance cannot be verified as the study is not submitted in the registration dossier for the registered substance.

In the absence of such information, the hypothesis according to which the properties of the substances are likely to be similar for the endpoint under consideration cannot be verified. Therefore, ECHA considers that you have not provided an adequate basis for predicting the properties of the registered substance from the source substances as required by the provisions of Annex XI, Section 1.5 of the REACH Regulation.

Adequacy of the source study

Annex XI, Section 1.5 requires that the source study(ies) used in a read-across approach should provide results that are adequate for classification and labelling, should have an adequate and reliable coverage of the key parameters and an exposure duration at least matching these parameters in the corresponding test method according to Article 13(3) of the REACH Regulation.

ECHA observes that in your read-across approach you have used the key study ([redacted]., 1998) on the analogue substance N-[3-(dimethylamino)propyl]-N,N',N'-trimethylpropane-1,3-diamine (EC No 223-362-3, CAS No 3855-32-1).

However, ECHA observes deficiencies in the robust study summary for the key study conducted with the analogue substance. For a test according to OECD TG 203 to be valid the following conditions should be fulfilled:

1) the mortality in the control(s) should not exceed 10% (or one fish if less than 10 fish are used) at the end of the test;
2) constant conditions should be maintained as far as possible throughout the test and, if necessary, semi-static or flow-through procedures should be used;
3) the dissolved oxygen concentration must have been at least 60 per cent of air saturation value throughout the test;
4) there must be evidence that the concentration of the substance being tested has been satisfactorily maintained, and preferable it should be at least 80 per cent of the nominal concentration throughout the test. If the deviation from the nominal concentration is greater than 20 per cent, results should be based on the measured concentration.

In your robust study summary, you have not reported the results of the mortality of the controls. Also you have not reported the dissolved oxygen concentrations; you only mention that "no aeration" was done during the test. In absence of this information, ECHA cannot verify whether all the validity criteria described in OECD TG 203 have been fulfilled for the key study.

Furthermore, the average zebra fish length at the study initiation 3.4 cm (range 2.7 - 3.7 cm), that you reported, is higher than the OECD 203 test guideline recommendation for the zebra fish (2.0 ± 1.0 cm). However, you have not provided any explanation or justification

whether this or any other possible deviations from the OECD 203 test guideline's recommendations affected the reliability of the results. In the absence of this information, it is not possible for ECHA to evaluate the reliability of this study.

In conclusion, ECHA considers that your adaptation does not meet the general rule for adaptation of Annex XI, Section 1.5.

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

In addition to the key study conducted with the analogue substance, you have submitted a supporting study with the registered substance according to test guideline JIS K-0102, as described above. Based on this supporting study you report a 48-h LC50 of 430 mg/L for *Oryzias latipes*.
ECHA notes that this study guideline is not a test method laid down in a Commission Regulation or other international test methods recognised by the Commission or the Agency as being appropriate. Therefore, ECHA has evaluated this information according to Annex XI Section 1.1.2. ECHA notes that the study duration, which you have reported to be 48-h, is shorter than the exposure period expected from a acute toxicity study on fish performed according to the OECD TG 203, which is 96-h. Therefore, ECHA considers that this study does not fulfil the requirement of Annex XI, Section 1.1.2. of the REACH Regulation for an exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3). Therefore, the supporting study with the registered substance does not fulfil the information requirement.

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

According to ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017) fish acute toxicity test (test method EU C.1. / OECD TG 203) is the preferred test to cover the standard information requirement of Annex VIII, Section 9.1.3.

In your comments to the draft decision you indicated an intention to perform the requested short-term toxicity test on fish.

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, acute toxicity test (test method: EU C.1./OECD TG 203).

6. and 7. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: Daphnia magna reproduction test, EU C.20./OECD TG 211), and 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).

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

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

You have sought to adapt these information requirements according to Annex IX, Sections 9.1.5. and 9.1.6 column 2 . You provided the following justification for both adaptations: "*According to Regulation (EC) No.1907/2006, Annexes VIII and IX, Column 2, long-term aquatic toxicity testing shall be conducted if the substance is poorly soluble in water, or if the chemical safety assessment indicates the need to investigate further the effects on aquatic organisms. The substance is soluble in water, and the chemical safety assessment indicated that aquatic exposures do not require further investigation; the risk characterisation ratios for surface water are below one. Therefore, in accordance with Annex I, the risks are considered to be controlled, and long-term toxicity testing of [*fish/ aquatic invertebrates] *is not indicated.*" However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Sections 9.1.5 and 9.1.6 due to following reasons. The results for short-term toxicity to fish (Annex VIII, Section 9.1.3.) used in your chemical safety assessment (CSA) are not reliable, as explained in request 5 above. As a result, also the PNEC derivation and consequent risk characterisation are currently not reliable. Therefore, the CSA cannot currently be used to adapt the current information requirement.

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

As explained above, the information provided on these endpoints 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 3.0, February 2016):

- the *Daphnia magna* reproduction test (test method: EU C.20/OECD TG 211) is the preferred test to cover the standard information requirement of Annex IX, section 9.1.5.
- the fish early-life stage 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.

Regarding the long-term toxicity testing on fish pursuant to Annex IX, section 9.1.6.1, ECHA considers that the FELS toxicity test according to OECD TG 210 is the most sensitive of the standard fish tests available as it covers several life stages of the fish from the newly fertilised egg, through hatch to early stages of growth and should therefore be used (see ECHA *Guidance on information requirements and chemical safety assessment* (version 3.0, February 2016), Chapter R7b, Figure R.7.8-4). The test method OECD TG 210 is also the only suitable test currently available for examining the potential toxic effects of bioaccumulation (ECHA Guidance Chapter R7b, version 3.0, February 2016). For these

reasons, ECHA considers the FELS toxicity test using the test method OECD TG 210 as most appropriate and suitable.

In your comments to the draft decision you indicated an intention to perform either long-term toxicity testing on fish or on *Daphnia*. You indicated that you will consider the results from the requested short-term toxicity study on fish (section 5 to this decision) to determine the relative species sensitivity and to decide which requested long-term study you will perform.

ECHA considers that you should 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. If 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. In case either fish or invertebrates is shown subtantially less sensitive, there is no further testing needed for the less sensitive species.

If you come to the conclusion that no further investigation of effects on aquatic organisms is required, you shall update your technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex IX, 9.1.5 and 9.1.6. taking into account the new data generated by the short-term toxicity studies requested by the present decision.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, based on the results of the short-term toxicity tests in sections 2 – 3 above, you are you are requested to submit the following information derived with the registered substance subject to the present decision: Long-term toxicity testing on aquatic invertebrates (Annex IX, 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211) and/or Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.; test method: Fish, early-life stage toxicity test, OECD 210).

Note for your consideration for aquatic testing

Due to the ionising properties of the registered 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 3.0, February 2016), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

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 26 April 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 proposals for amendment.

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

Appendix 3: Further information, observations and technical guidance

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

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

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.