Helsinki, 2 September 2020

**Addressees**
Registrants of JS_102-60-3 listed in the last Appendix of this decision

**Date of submission for the jointly submitted dossier subject of this decision**
30/10/2017

**Registered substance subject to this decision, hereafter 'the Substance'**
Substance name: 1,1',1'',1'''-ethylenedinitrilotetrapropan-2-ol
EC number: 203-041-4
CAS number: 102-60-3

**Decision number:** [Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/D)]

## DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***8 December 2023***.

### A. Requirements applicable to all the Registrants subject to Annex VII of REACH

1. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method EU C.2./OECD TG 202) with the Substance

2. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method EU C.3./OECD TG 201) with the Substance

### B. Requirements applicable to all the Registrants subject to Annex VIII of REACH

1. In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) with the Substance

2. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method OECD TG 476 or TG 490) if a negative result in Annex VIII, Section 8.4.2. is obtained with the Substance

3. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method OECD TG 203) with the Substance

### C. Requirements applicable to all the Registrants subject to Annex IX of REACH[1]

1. 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 Substance

2. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test

[1] Testing required under this Annex can only be started or performed after the decision has been adopted according to Article 51.

method EU C.20./OECD TG 211) with the Substance

3. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method OECD TG 210) with the Substance

**D. Requirements applicable to all the Registrants subject to Annex X of REACH[1]**

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method OECD TG 414) in a second species (rabbit or rat), oral route with the Substance.

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route specified as follows

   - Ten weeks premating exposure duration for the parental (P0) generation;
   - Dose level setting shall aim to induce systemic toxicity at the highest dose level;
   - Cohort 1A (Reproductive toxicity);
   - Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;
   - Cohorts 2A and 2B (Developmental neurotoxicity); with the Substance.

   You must report the study performed according to the above specifications. Any expansion of the study must be scientifically justified.

**Conditions to comply with the requested information**

Each addressee of this decision is bound by the requests for information corresponding to the REACH Annexes applicable to their own registered tonnage of the Substance at the time of evaluation of the jointly submitted dossier.
To identify your legal obligations, please refer to the following:

- you have to comply with the requirements of Annex VII of REACH, if you have registered a substance at 1-10 tonnes per annum (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- you have to comply with the requirements of Annexes VII and VIII of REACH, if you have registered a substance at 10-100 tpa;
- you have to comply with the requirements of Annexes VII, VIII and IX of REACH, if you have registered a substance at 100-1000 tpa;
- you have to comply with the requirements of Annexes VII to X of REACH, if you have registered a substance at above 1000 tpa.

Registrants are only required to share the costs of information that they must submit to fulfil the information requirements for their registration.

The Appendix on general considerations addresses issues relevant for several requests while the other Appendices state the reasons for the requests for information to fulfil the requirements set out in the respective Annexes of REACH.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information. The timeline has been set to allow for sequential testing where relevant.

**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[2] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[2] 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 on general considerations**

## (i) Assessment of the Grouping of substances and read-across approach under Annex XI, Section 1.5.

You seek to adapt the following standard information requirements by applying (a) read-across approach(es) in accordance with Annex XI, Section 1.5:

- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)
- Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

ECHA has considered the scientific and regulatory validity of your read-across approach(es) in general before assessing the specific standard information requirements in the following appendices.

### Grouping of substances and read-across approach

Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. 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 (addressed under 'Assessment of prediction(s)').

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance[3] and related documents[4, 5].

### A. Predictions for toxicological and ecotoxicological properties

You have provided the following reasoning for the prediction of toxicological properties:

*"the report [...] identifies common breakdown products and functionalities within a given grouping category of NLP polyols".* You have provided studies conducted with the structurally similar substance, "*Ethylenediamine, ethoxylated and propoxylated*", EC 500-047-1 as source substance [2, below].

You have provided the following read-across justification for aquatic toxicity endpoints in the Section 7.1 of CSR:

[3] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals. 2008 (May) ECHA, Helsinki. 134. pp. Available online: https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf/77f49f81-b76d-40ab-8513-4f3a533b6ac9

[4] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)

[5] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://doi.org/10.2823/794394

*"These substances exhibit a remarkable uniformity in the physical/chemical properties which influence their fate and distribution in the environment. All NLP polyols have a full acute aquatic ecotoxicity dataset and do not exhibit acute toxicity below 100 mg/L. However, differentiation in chronic invertebrate toxicity is apparent and is based on the alcohol- or amino- starter molecules used to prepare these NLP polyols. A sub-grouping based on (i) aliphatic alcohol and amine NLP polyols, (ii) EDA- (ethylenediamine) based amino NLP polyols and (iii) o-TDA- (ortho-diaminotoluene) based aromatic NLP polyols is justified ([redacted] 2010) and toxicity is expected to be similar between substances within each of these categories.".*

You read across to your Substance from the structurally similar substances:
[1] Ethylenediamine, propoxylated (EC 500-035-6); and
[2] Ethylenediamine, ethoxylated and propoxylated (EC 500-047-1).

ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted to be quantitatively equal to those of the source substance.

Furthermore, there are two other documents provided in IUCLID registration dossier, Section 13 which are aiming *"to evaluate the toxicology and toxicokinetics data available for certain NLP Polyols, their core substance (initiating agent) and their repeating units in order to:*

- *Provide justification for read across of data for groupings of NLP polyols*
- *Provide toxicokinetics assessments for inclusion in the dossiers for each NLP polyol group."*

ECHA did not consider these documents to be relevant for the read-across because they do not refer to the Substance.

ECHA notes the following shortcomings with regards to predictions of hazard properties of the substance.

*Absence of read-across documentation*

Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide a justification for the read-across including a hypothesis, explanation of the rationale for the prediction of properties and robust study summary(ies) of the source study(ies).[6]

You have provided studies conducted with other substances than your Substance in order to comply with the REACH information requirements. You have not provided documentation as to why this information is relevant for your Substance. Instead, you have provided documentation as to why this information is relevant for other Substances,"Ethylenediamine, propoxylated, 1-5.5 moles" and "Ethylenediamine, propoxylated, 3-4 moles", both with EC number 500-035-6.

In the absence of documentation relevant for your Substance, ECHA cannot verify that the properties of your Substance can be predicted from the data on the source substance(s).

*Missing well-founded hypothesis for read-across*

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

[6] Read-across assessment framework, ECHA 2017

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).
A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the source substance(s) and your Substance[7]. It should explain why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern.

Your read-across justification does neither include comparison of the structural similarity nor of the physicochemical properties between the source substance(s) and your Substance.

Furthermore, while structural similarity is a prerequisite for applying the grouping and read-across approach, it does not necessarily lead to predictable or similar toxicological or ecotoxicological properties. You have not provided a well-founded hypothesis to establish a reliable prediction for genetic and aquatic toxicity, based on recognition of the structural similarities and differences between the source substance(s) and your Substance.

*Missing supporting information/bridging studies to compare properties*

Annex XI, Section 1.5 of the REACH Regulation states that "*adequate and reliable documentation of the applied method shall be provided*". Within this documentation "*it is important to provide supporting information to strengthen the rationale for the read-across*"[8]. The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s).

"*Adequate and reliable documentation*" must include bridging studies to compare properties of the target and source substances. As indicated above, your read-across hypothesis is based on the assumption that the structurally similar target and source substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the target and source substance is necessary to confirm that both substance cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the target and the source substances.

In the registration dossier you have provided studies on aquatic toxicity and genotoxicity in mammalian cells only with the source substances. The data set reported in the technical dossier does not include relevant, reliable and adequate information for the target substance to support your read-across hypothesis.

In the absence of such information, you have not established that the target and the source substances are likely to have similar properties. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

*Quality of the studies with source substance(s) for environmental endpoints*

As required in Annex XI, Section 1.5. of the REACH Regulation, source studies should be adequate for the purpose of classification and labelling and/or risk assessment, have adequate and reliable coverage of the key parameters and cover an exposure duration comparable to

[7] *Guidance on information requirements and chemical safety assessment*, Chapter R.6: QSARs and grouping of chemicals.
[8] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

or longer than the corresponding test method referred to in Article 13(3), and adequate and reliable documentation of the applied method shall be provided.

Based on the information provided in the technical registration dossier the Substance at environmentally relevant pHs is present in the ionised forms, i.e. possess high potential for adsorption. As you have stated in the read-across justification the target and the source "*substances exhibit a remarkable uniformity in the physical/chemical properties*". Thus, ECHA understands that the source substances also have high potential for adsorption.

As noted in the ECHA Guidance Chapter R.7b and OECD Guidance Document on Aqueous-phase Aquatic Toxicity Testing of Difficult Chemicals, ENV/JM/MONO (2000)6/REV1, one of the key issues for difficult to test substances is the ability to quantify actual exposure of the test organisms to the test substance. Thus, analytical verification of the exposure concentrations during the testing period is necessary for such type of substances which may not be stable in the test solution. It is supported by the information provided for the algae toxicity study performed with source substance [1], where "*Measured concentrations ranged from 76.9 - 130 % of nominal values at 0 hours, and from 60.7 - 94 % of nominal values at 72 hours, respectively*".

Analytical monitoring of exposure concentrations of the test item in the short-term aquatic toxicity studies with fish and Daphnia performed with source substance [1] was not performed. Therefore, ECHA considers that such aquatic toxicity studies which were performed without analytical monitoring of exposure concentrations are not reliable.

**B. Conclusions on the grouping of substances and read-across approach for toxicological and ecotoxicological properties**

As explained above your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. Therefore, your adaptation for toxicological and ecotoxicological properties is rejected and it is necessary to perform testing on your Substance.

**(ii) Assessment of further adaptations under Annex XI**

*Weight of evidence adaptation*
You seek to adapt the following standard information requirements:

- Pre-natal developmental toxicity study in a first species (Annex IX, Section 8.7.2)
- Pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2)
- Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3)

While an adaptation was not specifically indicated by you, ECHA has evaluated the provided information according to Annex XI, Section 1.2.

You have provided the following information to support your adaptation:

1. An experimental study (combined repeated dose toxicity with the screening for reproductive/developmental study) according to guideline OECD TG 422 with the Substance
2. You have justified the adaptation as follows, referring partly to read-across from the core substance and repeating unit: "*Ethylenediamine, +4PO is not classifiable as hazardous in respect to its reproductive toxicity. There is sufficient information from a qualitative and quantitative understanding of the toxicological properties of the core substance, the repeating unit, and a substance specific reliable OECD 422 study, such that testing for reproductive toxicity is not necessary. In view of this, no further testing is proposed.*"

Annex XI, Section 1.2 states that there may be sufficient weight of evidence (WoE) from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

*Prenatal developmental toxicity*

In order to allow concluding on no prenatal developmental toxicity in two species for the Substance in a weight of evidence adaptation, the justification must cover the key elements (parameters) foreseen to be investigated in an OECD TG 414 study in two species.
The key parameter(s) of this test guideline include e.g. external, skeletal and soft tissue alterations (variations and malformations).

ECHA has assed to what extent the information submitted enables a conclusion of hazardous properties for prenatal developmental toxicity and identified the following deficiencies:

The OECD TG 422 study with the Substance does not provide information on external, skeletal and soft tissue alterations (variations and malformations) as foreseen to be investigated in OECD TG 414. It does not provide information in two species. Your claim that "*There is sufficient information from a qualitative and quantitative understanding of the toxicological properties of the core substance, the repeating unit,...*" (proposed source substance(s) for a read-across) has not been substantiated regarding prenatal developmental toxicity.

In conclusion, none of the pieces of information alone or together allows to conclude whether the Substance has or has not hazardous properties related to prenatal developmental toxicity. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

*Reproductive toxicity (sexual function and fertility and toxicity to offspring)*

In order to allow concluding on no reproductive toxicity (sexual function and fertility and toxicity to offspring) for the Substance in a weight of evidence adaptation, the justification must cover the key elements (parameters) foreseen to be investigated in an extended one-generation reproductive toxicity study (OECD TG 443) with the specified study design as requested in this decision (Cohorts 1A and 1B with developmental neurotoxicity (Cohorts 2A and 2B)).

Exposure must cover all the life stages foreseen to be investigated in OECD TG 443 as specifed in the request (D.2). Information on sexual function and fertility (functional fertility and histopathology of reproductive organs and tissues) after at least ten weeks premating exposure duration must be covered in parental P0 animals as indicated in OECD TG 443. Information on toxicity to the offspring after exposure from *in utero*, peri- and postnatal periods up to adulthood must be covered as foreseen to be investigated in OECD TG 443.

Information must address the histopathology of reproductive organs and tissues in F1 generation in adulthood. Information on developmental neurotoxicity must be addressed because the column 2 criteria in section 8.7.3 at Annex IX/X are met. The information must allow to conclude on properties foreseen to be investigated in Cohorts 2A and 2B of the OECD TG 443 after similar exposure duration.

ECHA has assessed to what extent the information submitted enables a conclusion of "reproductive toxicity" and identified the following deficiencies:

Exposure and information does not cover all relevant life stages foreseen to be investigated in OECD 443. Information on developmental neurotoxicity is not available although the criteria in column 2, Section 8.7.3, Annex IX/X are met.

The OECD TG 422 study investigates effects due to exposure during limited premating (2 weeks), mating, gestation, delivery and a limited time during lactation. Your claim "*There is sufficient information from a qualitative and quantitative understanding of the toxicological properties of the core substance, the repeating unit, …"* (proposed source substance(s) for a read-across) has not been substantiated regarding hazardous properties to sexual function and fertility and toxicity to offspring.

Information on sexual function and fertility in parental P0 animals is not available after ten weeks premating exposure duration.

Therefore the information does not allow to assess 'sexual function and fertility' in the P0 generation with sufficient premating exposure duration to ensure steady state of the Substance in parental animals and the coverage of full spermatogenesis and folliculogenesis before mating. None of the available information address the 'toxicity to offspring' with regard post-natal investigations of the F1 generation up to adulthood. There is no information available on histopathology of reproductive organs and tissues in F1 generation in the dossier. You provide no source of information on developmental neurotoxicity.

In conclusion, none of the pieces of information alone or together allows to conclude whether the Substance has or has not hazardous properties related to sexual function and fertility or toxicity to offspring. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

**Appendix A: Reasons for the requests to comply with Annex VII of REACH**

In accordance with Articles 10(a) and 12(1) of the REACH, a technical dossier registered at 1 to 10 tonnes or more per year must contain, as a minimum, the information specified in Annex VII to the REACH.

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

Short-term toxicity testing on aquatic invertebrates is a standard information requirement in Annex VII to REACH.

You have provided one short-term toxicity to aquatic invertebrates key study performed with the analogue substance [1] (without analytical monitoring of exposure concentrations of the test item) in the registration dossier.

As already explained in the Appendix on general considerations your adaptation according to Annex XI, Section 1.5 is rejected and aquatic toxicity studies with the analogue substance [1] which were performed without analytical monitoring of exposure concentrations are not reliable. Therefore, the information requirement is not fulfilled.

Consequently, there is a data gap that needs to be filled in.

In your comments on the draft decision you agree to this request.

2. **Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)**

Growth inhibition study aquatic plants is a standard information requirement in Annex VII to REACH.

You have provided one algal inhibition key study performed with the analogue substance [1] in the registration dossier.

As already explained in the Appendix on general considerations your adaptation according to Annex XI, Section 1.5 is rejected. Therefore, the information requirement is not fulfilled.

Consequently, there is a data gap that needs to be filled in.

In your comments on the draft decision you agree to this request.

**Appendix B: Reasons for the requests to comply with Annex VIII of REACH**

In accordance with Articles 10(a) and 12(1) of the REACH, a technical dossier registered at 10 to 100 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII and VIII to the REACH.

1. **In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)**

An *In vitro* cytogenicity study in mammalian cells or an *In vitro* micronucleus study is a standard information requirement in Annex VIII to REACH.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5.

As explained in the Appendix on general considerations your adaptation is rejected.

Therefore, the information requirement is not fulfilled.

In your comments on the draft decision you agree to this request.

2. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)**

An *in vitro* gene mutation study in mammalian cells is a standard information requirement in Annex VIII to REACH in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5.

As explained in the Appendix on general considerations your adaptation is rejected.

Therefore, the information requirement is not fulfilled.

In your comments on the draft decision you agree to this request.

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

Short-term toxicity testing on fish is a standard information requirement in Annex VIII to REACH.

You have provided three short-term toxicity to fish studies, all performed with the analogue substance [1] and without analytical monitoring of exposure concentrations of the test item, in the registration dossier.

As already explained in the Appendix on general considerations your adaptation according to Annex XI, Section 1.5 is rejected and aquatic toxicity studies with analogue substance [1] which were performed without analytical monitoring of exposure concentrations are not reliable. Therefore, the information requirement is not fulfilled.

Consequently, there is a data gap that needs to be filled in.
In your comments on the draft decision you agree to this request.

**Appendix C: Reasons for the requests to comply with Annex IX of REACH**

In accordance with Articles 10(a) and 12(1) of the REACH, a technical dossier registered at 100 to 1000 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII-IX to the REACH.

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

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX to REACH.

You have provided an OECD TG 422 study (2009) with the Substance as basis of an adaptation (waiver).

ECHA has assessed your adaptation according to Annex XI, Section 1.2. (weight of evidence) of REACH. As explained in the Appendix on general considerations your adaptation is rejected.

In your comments on the draft decision you indicate your intention to potentially adapt this information requirement by a read-across adaptation, depending on the outcome of a combined repeated dose toxicity and screening for reproductive/developmental toxicity study (OECD TG 422) with another substance (Ethylenediamine, propoxylated (CAS 25214-63-5)).

However, you have not provided with your comments a hypothesis, justification and supporting (experimental) data to support a read-across adaptation. Therefore, it is not possible to conduct an evaluation of the potential read-across adaptation referred to in your comments in the absence of any documentation and of any explanation of the relevance to the prediction of properties. It is in your discretion to provide the necessary supporting information in order to justify your read-across adaptation. If you do so, you are responsible for demonstrating the fulfilment of the requirements of Section 1.5 of Annex XI to REACH. Your updated dossier will be evaluated after the deadline of this decision has passed.

Therefore, the information requirement is not fulfilled.

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[9] administration of the Substance.

*Information on second species*

Information on second species is an information requirement for your substance in case of concern.

Annex IX, Section 8.7.2., column 2 provides that the decision on the need to perform a PNDT study on a second species at a tonnage level of 100 to 1000 tonnes per year should be based on the outcome of the PNDT study on a first species and all other relevant and available data.

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

Long-term toxicity testing on aquatic invertebrates is a standard information requirement in Annex IX to REACH.

[9] ECHA Guidance R.7a, Section R.7.6.2.3.2.

You have provided one long-term toxicity to aquatic invertebrates study performed with the analogue substance [2] in the registration dossier.

As already explained in the Appendix on general considerations your adaptation according to Annex XI, Section 1.5 is rejected. Therefore, the information requirement is not fulfilled.

In your comments on the draft decision you indicate that "*in case the new acute test data support the read across*" which you have proposed in the registration dossier, you would "*keep this read across approach by providing a suitable analogue justification document.*"

ECHA notes that it is in your discretion to provide the necessary supporting information in order to justify your read-across adaptation. If you do so, you are responsible for demonstrating the fulfilment of the requirements of Section 1.5 of Annex XI to REACH. Your updated dossier will be evaluated after the deadline of this decision has passed.

Consequently, there is a data gap that needs to be filled in.

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

Long-term toxicity testing on fish is a standard information requirement in Annex IX to REACH.

You have provided an adaptation based on column 2 of Annex IX, section 9.1., summarised as follows: "...*The hazard assessment of the substance reveals neither a need to classify the substance as dangerous for the environment, nor is it a PBT or vPvB substance, nor are there any further indications that the substance may be hazardous to the environment...*".

In order to adapt the information requirement for long-term toxicity to fish based on Annex IX, Section 9.1, Column 2, the Chemical Safety Assessment (CSA) needs to demonstrate that risks towards the aquatic compartment arising from the use of the Substance are controlled (as per Annex I, section 0.1).The Chemical Safety Assessment (CSA) needs to assess and document that risks arising from the Substance are controlled and demonstrate that there is no need to conduct further testing (Annex I, Section 0.1; Annex IX, Section 9.1, Column 2).

In particular, you need to take into account of the following elements in your justification:

- all relevant hazard information from your registration dossier,
- the outcome of the exposure assessment in relation to the uses of the Substance,
- the outcome of the PBT/vPvB assessment including information on relevant degradation products and constituents present in concentration at or above 0.1% (w/w).

As specified in requests A.1. – A.2. & B.4. & C.2., the data on Short-term toxicity testing on aquatic invertebrates, Growth inhibition study aquatic plants, Short-term toxicity testing on fish, Long-term toxicity testing on aquatic invertebrates are not compliant. Hence your dossier currently does not include adequate information to characterize the hazard property of the Substance.

Therefore your Chemical Safety Assessment does not demonstrate that the risks of the Substance are adequately controlled. As a consequence, your adaptation is rejected as it does not meet the specific rules for adaptation of Annex IX, Section 9.1.5., Column 2.

Consequently, there is a data gap that needs to be filled in.

As reliable information neither on the short-term toxicity to fish nor to invertebrates is available, neither fish nor invertebrates are shown to be substantially more sensitive than

other trophic levels (i.e., fish, invertebrates, algae). According to the integrated testing strategy (ITS) (ECHA Guidance R.7b,Section R.7.8.5 including Figure R.7.8-4), if necessary, the long-term *Daphnia* toxicity study is to be conducted first. If based on the results of that study and the application of a relevant assessment factor no risks are observed (PEC/PNEC<1), the long-term fish study may not need to be conducted. However, if a risk is indicated, the long-term fish study needs to be conducted.

In your comments on the draft decision you indicate that the need to perform the study in this request will be decided according to the integrated testing strategy when all data necessary are available. ECHA will evaluate your updated dossier after the deadline set out in this decision has passed.

**Appendix D: Reasons for the requests to comply with Annex X of REACH**

In accordance with Articles 10(a) and 12(1) of the REACH, a technical dossier at tonnage above 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII-X to the REACH.

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

Pre-natal developmental toxicity (PNDT) studies (OECD TG 414) in two species is a standard information requirement under Annex X to REACH.

You have provided an OECD TG 422 study (2009) with the Substance as basis for an adaptation (waiver). ECHA has assessed your adaptation according to Annex XI, Section 1.2. (weight of evidence) of REACH.

As explained in the Appendix on general considerations your adaptation is rejected.

You have not provided information on pre-natal developmental toxicity in a second species.

In your comments on the draft decision you indicate your intention to potentially adapt this information requirement by a read-across adaptation, depending on the outcome of a combined repeated dose toxicity and screening for reproductive/developmental toxicity study (OECD TG 422) with another substance (Ethylenediamine, propoxylated (CAS 25214-63-5)).

However, as explained in Section C.1 above, it is not possible to conduct an evaluation of the potential read-across adaptation referred to in your comments in absence of any documentation and any explanation of the relevance. It is in your discretion to provide the necessary supporting information in order to justify your read-across adaptation. If you do so, you are responsible for demonstrating the fulfilment of the requirements of Section 1.5 of Annex XI to REACH. Your updated dossier will be evaluated after the deadline of this decision has passed.

Therefore, the information requirement is not fulfilled.

A PNDT study according to the OECD TG 414 study must be performed in rabbit or rat as the preferred second species, depending on the species tested in the first PNDT study (request C.1. in this decision). The study must be performed with oral[10] administration of the Substance.

2. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.);**

The basic test design of an Extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is a standard information requirement under Annex X to REACH. Furthermore Column 2 of Section 8.7.3. defines when the study design needs to be expanded.

You have provided an OECD TG 422 study (2009) with the Substance as basis for an adaptation (waiver). ECHA has assessed your adaptation according to Annex XI, Section 1.2. (weight of evidence) of REACH.

As explained in the Appendix on general considerations your adaptation is rejected.

[10] ECHA Guidance R.7a, Section R.7.6.2.3.2.

In your comments on the draft decision you indicate your intention to potentially adapt this information requirement by a read-across adaptation, depending on the outcome of a combined repeated dose toxicity and screening for reproductive/developmental toxicity study (OECD TG 422) with another substance (Ethylenediamine, propoxylated (CAS 25214-63-5)).

However, as explained in Section C.1 above, it is not possible to conduct an evaluation of the potential read-across adaptation referred to in your comments in the absence of any documentation and any explanation of the relevance to the prediction of properties. It is in your discretion to provide the necessary supporting information in order to justify your read-across adaptation. If you do so, you are responsible for demonstrating the fulfilment of the requirements of Section 1.5 of Annex XI to REACH. Your updated dossier will be evaluated after the deadline of this decision has passed.

Therefore, the information requirement is not fulfilled.

The extended one-generation reproductive toxicity study according to OECD TG 443 is appropriate to fulfil the information requirement.

*The specifications for the study design*

*Premating exposure duration and dose-level setting*

The length of premating exposure period must be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required to obtain results adequate for classification and labelling and /or risk assessment. There is no substance specific information in the dossier supporting shorter premating exposure duration.[1]

Therefore, the requested premating exposure duration is ten weeks.

The highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

If there is no relevant data to be used for dose level setting, it is recommended that range-finding results are reported with the main study.

You have to provide a justification with your study results that demonstrates that the dose level selection meets the conditions described above.

*Cohorts 1A and 1B*

Cohorts 1A and 1B belong to the basic study design and shall be included.

*Cohorts 2A and 2B*

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity.

Existing information on the Substance itself derived from the available *in vivo* study (OECD TG 422, 2009) show evidence of neurotoxicity in the central nervous system. A *vacuolation*

*of epithelial cells of the lateral ventricles of the brain* was observed in all animals of the high dose in the absence of further toxicity.

Therefore, the developmental neurotoxicity Cohorts 2A and 2B need to be conducted.

*Species and route selection*

The study must be performed in rats with oral[11] administration.

*Further expansion of the study design*

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B and/or Cohort 3 if relevant information becomes available from other studies or during the conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance[12].

[11] ECHA Guidance R.7a, Section R.7.6.2.3.2.
[12] ECHA Guidance R.7a, Section R.7.6.

## Appendix E: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of the REACH Regulation.

The compliance check was initiated on 2 October 2018.

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

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

ECHA took into account your comments and removed one request (Justification for an adaptation of a Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.) and amended the deadline.

### Deadline to submit the requested information in this decision

The timeline indicated in the draft decision to provide the information requested was 30 months from the date of adoption of the decision.

In your comments on the draft decision, you requested the timeline to be set to 42 months. You justified your request stating:

a) that the capacity of test facilities was limited, and that
b) additional time was needed to refine the testing strategy with respect to the proposed read-across approach by conducting an additional study.

As regards the limited capacity of the test facilities, you submitted supporting information to justify your request. ECHA considers on the basis of this information that six additional months are needed for the testing.

As regards additional time to refine the testing strategy with respect to the proposed read-across approach, ECHA observes that the additional test you propose is not requested in this decision on the Substance. The validity of the potential adaptation proposed by you with your comments cannot be assessed at the moment as explained under Appendix C Section 1 of this decision. It is at your discretion to perform the abovementioned screening for reproductive/developmental toxicity study, which can be commenced at any point in time. However, since the present decision does not require you to perform such test, this cannot be taken into account in the calculation of its deadline.

Furthermore, the deadline set by ECHA allows sequential testing for the requests C.1 and D.2 in the decision. In addition, the tests under B1, B2, and C1; as well as D1 and D2; may be conducted in parallel.

Therefore, ECHA has partially granted the request and set the deadline to 36 months.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

## Appendix F: Observations and technical guidance

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

**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 the Member States.

**3.** Test guidelines, GLP requirements and reporting

Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses shall be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

Under Article 10 (a) (vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide: 'How to report robust study summaries'[13].

**4.** Test material

Selection of the test material(s) for UVCB substances

The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

While selecting the test material you must take into account the impact of each constituent/impurity on the test results for the endpoint to be assessed. For example, if a constituent/impurity of the Substance is known to have an impact on (eco)toxicity, the selected test material must contain that constituent/impurity. Any constituents that have harmonised classification and labelling according to the CLP Regulation (Regulation (EC) No 1272/2008) must be identified and quantified using the appropriate analytical methods.

The OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 11 [ENV/MC/CHEM(98)16] requires a careful identification of the test material and description of its characteristics. In addition, the Test Methods Regulation (EU) 440/2008, as amended by Regulation (EU) 2016/266, requires that "*if the test method is used for the testing of a* [...] *UVCB* [...] *sufficient information on its composition should be made available, as far as possible, e.g. by the chemical identity of its constituents, their quantitative occurrence, and relevant properties of the constituents*".

[13] https://echa.europa.eu/practical-guides

In order to meet this requirement, all the constituents of the test material used for each test must be identified as far as possible. For each constituent the concentration value in the test material must be reported in the Test material section of the endpoint study record.

Technical Reporting of the test material for UVCB substances

The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and indication of the regio-and diastereo isomers and their concentration values and other parameters relevant for the property to be tested. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers" on the ECHA website[14].

**5.** List of references of the ECHA Guidance and other guidance/ reference documents[15]

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 in this decision.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[16]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

[14] https://echa.europa.eu/manuals
[15] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[16] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

OECD Guidance documents[17]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.
Guidance Document supporting the OECD TG 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD151.

[17] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

**Appendix G: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them**

| Registrant Name | Registration number | (Highest) Data requirements to be fulfilled |
|---|---|---|
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.