~~Confidential~~

Helsinki, 15 March 2022

Addressees
Registrant(s) of Dioctylether as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
30/06/2021

Registered substance subject to this decision ("the Substance")
Substance name: Dioctyl ether
EC number: 211-112-6

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***20 June 2025***.

Requested information must be generated using the Substance unless otherwise specified.

A. Information required from all the Registrants subject to Annex VII of REACH

1. Long-term toxicity testing on aquatic invertebrates also requested below (triggered by Annex VII, Section 9.1.1., column 2)

B. Information required from all the Registrants subject to Annex VIII of REACH

1. Long-term toxicity testing on fish also requested below (triggered by Annex VIII, Section 9.1.3., column 2)

C. Information required from all the Registrants subject to Annex IX of REACH

1. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: EU C.20./OECD TG 211)

2. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: OECD TG 210)

D. Information required from all the Registrants subject to Annex X of REACH

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

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) by oral route, in rats, 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) with extension to mate the Cohort 1B animals to produce the F2 generation which shall be followed to weaning.**

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

Reasons for the request(s) are explained in the following appendices:

- Appendix entitled "Reasons common to several requests";
- Appendices entitled "Reasons to request information required under Annexes VII to X of REACH", respectively.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

For certain endpoints, ECHA requests the same study from registrants at different tonnages. In such cases, only the reasoning why the information is required at lower tonnages is provided in the corresponding Appendices. For the tonnage where the study is a standard information requirement, the full reasoning for the request including study design is given. Only one study is to be conducted; the registrants concerned must make every effort to reach an agreement as to who is to carry out the study on behalf of the other registrants under Article 53 of REACH.

How to comply with your information requirements

To comply with your information requirements you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Mike Rasenberg, Director of Hazard Assessment

[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 on Reasons common to several requests

(i) Assessment of your weight of evidence adaptation under Annex XI, Section 1.2.

You seek to adapt the following standard information requirements by applying (a) weight of evidence approaches in accordance with Annex XI, Section 1.2:

- 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.)
- Long-term toxicity testing on fish (triggered at Annex VIII, Section 9.1.3. and Annex IX, Section 9.1.6.)

ECHA has considered the scientific and regulatory validity of your weight of evidence approach in general before assessing the specific standard information requirements in the following appendices.

Annex XI, Section 1.2 states that there may be sufficient weight of evidence 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.

According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

You have provided summaries in separate endpoint study records for reproductive and developmental toxicity. In those summaries you briefly present each of the sources of information, describe the results and conclude that this read-across information can be used for weight of evidence to predict the toxicological properties of the Substance for reproductive toxicity: "*Results from a developmental toxicity study and a subchronic toxicity study obtained with dioctylether did not reveal any reason of concern for offspring and for parent animals with respect to developmental toxicity or fertility. Since significant scientific evidence for a lack of reprotoxic effects of the substance is drawn from these results, an extended one generation study is not expected to add any further relevant knowledge on this endpoint. In addition, three one generation studies performed with read across substances (diethyleneglycolethylether, DEGEE, CAS 111-90-0) and diethylenglycolbutylether, DEGBE, CAS 112-34-5) by the oral and dermal routes are also available." […] "Due to animal welfare aspects and/or laws, an additional study is therefore not warranted. In accordance with Section 1 of Annex XI, the extended one-generation reproductive toxicity study (as required in Section 8.7.3) is scientifically unjustified*."

And similarly for developmental toxicity: "*Teratogenicity studies in mice and rabbits (NTP, 1987a, b) obtained with Diethylene glycol diethyl ether (DEGDEE, CAS 112-36-7) failed to show any adverse effects on embryonic or foetal development, even at maternally toxic doses." […] "Dioctylether was already tested in a GLP guideline study for its teratogenic potential in one species without any effects. Due to animal welfare aspects and data from*

read across substances in other species, an additional study in a second species is therefore not warranted.".

For the environment, you have provided generic arguments for justifying data waiving for long-term toxicity to fish based mainly on other aquatic species (aquatic algae, lemna and Daphnia), without any weighing of the provided sources of information.

You have not included a justification for your weight of evidence adaptation, which would include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Your adaptation is rejected because lack of adequate and reliable (concise) documentation for justification and the information requirement is not fulfilled.

Irrespective of the above mentioned deficiencies on the documentation, which in itself could lead to the rejection of the adaptation, ECHA has assessed the provided sources of information.

Your weight of evidence adaptation has deficiencies that are common to all information requirements under consideration and also deficiencies that are specific for these information requirements individually. The common deficiencies are set out here, while the specific ones are set out under the information requirement concerned in the Appendices below.

Reliability of the provided information with analogue substances

ECHA understands that you intend to predict the **toxicological** properties of the Substance for the listed above endpoints, from data obtained with analogue substances in a read-across approach as part of your weight of evidence adaptation.

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 (addressed under 'Scope of the grouping'). 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 R.6. and related documents[2,3].

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 study(ies) on the source substance(s) (Guidance on IRs and CSA, Section R.6.2.6.2).

[2] 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)

[3] 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

In your registration dossier you refer to read across approach and a document "*Category Approach-Read across Bis(2 -ethoxyethyl)ether" (2013)* and conclude that "*these substances have been demonstrated to be similar in structure, physical/chemical properties and toxicological profile*". You have provided robust study summaries for studies conducted with other substances than the Substance in order to comply with the REACH information requirements. However, you have not provided documentation as to why this information is relevant for the Substance.

In the absence of such documentation, the properties of the Substance cannot be reliably predicted from the data on the source substances.

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the analogue substance.

Endpoint-specific shortcomings affecting the reliability

Further endpoint-specific shortcomings affecting the relevance and reliability of the weight of evidence approach are detailed in the reasoning in Appendices C and D.

Appendix A: Reasons to request information required under Annex VII of REACH

1. Long-term toxicity testing on aquatic invertebrates

Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII to REACH (Section 9.1.1.). Long-term toxicity testing on aquatic invertebrates must be considered (Section 9.1.1., Column 2) if the substance is poorly water soluble.

You have provided an OECD TG 211 study for the Substance.

We have assessed this information and identified the following issue:

Poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term tests does not give a true measure of toxicity for this type of substances and the long-term test is required. A substance is regarded as poorly water soluble if, for instance, it has a water solubility below 1 mg/L or below the detection limit of the analytical method of the test material (ECHA Guidance R.7.8.5).

You have provided information which indicates that the Substance is poorly water soluble. Based on an OECD TG 105 Key Study as well as a QSAR prediction submitted as a Supporting Study, you demonstrate that water solubility of the Substance is below 0.1 mg/L.

Therefore, the Substance is poorly water soluble and information on long-term toxicity on aquatic invertebrates must be provided.

The examination of the information provided, as well as the selection of the requested test and the test design are addressed under Appendix C.1.

ECHA notes in this respect that you have provided an adaptation based on the alleged presence of mitigating factors. This ground of adaptation (Annex VII, Section 9.1.1., Column 2, first indent) does not apply, however, when a long-term study must be considered because the substance is poorly water soluble under Annex VII Section 9.1.1., Column 2 last paragraph.

Appendix B: Reasons to request information required under Annex VIII of REACH

1. Long-term toxicity testing on fish

Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.). Long-term toxicity testing on fish must be considered (Section 9.1.3., Column 2) if the substance is poorly water soluble.

You have provided an ISO 7346-1 (Determination of the Acute Lethal Toxicity of Substances to a Freshwater Fish [Brachydanio rerio Hamilton-Buchanan (Teleostei, Cyprinidae)) study on short-term toxicity to fish and an adaptation for long-term toxicity to fish for the Substance.

We have assessed this information and identified the following issue:

Poorly water soluble substances require longer time to reach steady-state conditions. As a result, the short-term tests does not give a true measure of toxicity for this type of substances and the long-term test is required.

As already explained under Section A.1, the Substance is poorly water soluble and information on long-term toxicity on fish must be provided.

The examination of the information provided, as well as the selection of the requested test and the test design are addressed under Section C.2.

ECHA notes in this respect that you have provided an adaptation based on the alleged presence of mitigating factors. This ground of adaptation (Annex VIII, Section 9.1.3., Column 2, first indent) does not apply, however, when a long-term study must be considered because the substance is poorly water soluble under Annex VIII Section 9.1.3., Column 2 last paragraph.

Appendix C: Reasons to request information required under Annex IX of REACH

1. Long-term toxicity testing on aquatic invertebrates

Long term toxicity testing on aquatic invertebrates is an information requirement under Annex IX to REACH (Section 9.1.5.).

You have provided and OECD Guideline 211 (Daphnia magna Reproduction Test) for the Substance.

We have assessed this information and identified the following issue(s):

To fulfil the information requirement, a study must comply with the OECD TG 211 (Article 13(3) of REACH). Therefore, the following specifications must be met:

Validity criteria

- the percentage of mortality of the parent animals (female Daphnia) in the control is ≤ 20% at the end of the test;
- the mean number of living offspring produced per surviving parent animal in the control is ≥ 60 at the end of the test;

Technical specifications impacting the sensitivity/reliability of the test

- the test concentrations are below the limit of solubility of the test material in the dilution water;

Characterisation of exposure

- a reliable analytical method for the quantification of the test material in the test solutions with reported specificity, recovery efficiency, precision, limits of determination (i.e. detection and quantification) and working range must be available;
    1) in semi-static tests, if the concentration of the test material is not expected to remain within ± 20 % of the nominal concentration, then all test concentrations must be determined when freshly prepared and at the time of renewal on one occasion during each week of the test;

Reporting of the methodology and results

- the nominal test concentrations and the results of all analyses to determine the concentration of the test substance in the test vessels are reported;
- the full record of the daily production of living offspring during the test by each parent animal is provided;

Your registration dossier provides an OECD TG 211 showing the following:

Validity criteria

- the percentage of mortality of the parent animals in the control at the end of the test was 0%;
- the mean number of living offspring produced per parent animal surviving at the end of the test was 120.

However, whilst the biological values have been reported for the validity criteria, due to the non reliable analytical method (see below) no level of accuracy can be assigned to these values.

Characterisation of exposure

- you have not provided performance parameters of the analytical method (limits of determination (detection and quantification));

- you report that in the definitive study "*Regarding analytically determined concentrations, no reproducible values could be detected, probably due to the test substance's low solubility and high lipophilicity. Therefore, EC values were based on the nominal concentrations*".

  However, for the test with Lemna (see chapter 6.1.6 toxicity to aquatic plants other than algae) you were able to eliminate the potential shortcomings (analytics) with accurate/elaborated analytics in the range of media solubility. Furthermore, the test material is not expected to remain within +/- 20% of the nominal concentration considering that the measured concentrations of Dioctyl ether in the fresh test media were 67 to 94%. Therefore, based on the results of the Lemna study where the results were expressed as measured values, the effect concentration in the definitive long term Daphnia study must be expressed based on measured values as the behaviour of the substance in solution is expected to be the same.

Technical impacting the sensitivity/reliability of the test

- the test concentrations were 6.25, 12.5, 25, 50, 100 mg/L and the resulting effect concentration (i.e. LOEC for reproduction) was 25 mg/L; at the same time, you report in your dossier a limit of solubility of the test material in water of <0.1 mg/L;

Reporting of the methodology and results

- the results of the analyses to determine the concentration of the test substance in the test vessels are not provided (see previous point);
- the full record of the daily production of living offspring during the test by each parent animal is not provided;

Based on the above,

- the Substance is difficult to test (due to its low water solubility), there are critical methodological deficiencies and the characterisation of exposure all result in the rejection of the study results. More, specifically, based on the reported data, it is unclear what test concentrations were the test organisms exposed to. Consequently, it is also unclear, what is the actual effect concentration to which the effects seen in the test can be related.
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. Therefore, the requirements of OECD TG 211 are not met.

Study design

The Substance is difficult to test due to the low water solubility (< 0.1 mg/L). OECD TG 211 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 211. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

2. Long-term toxicity testing on fish.

Long-term toxicity testing on fish is an information requirement under Annex IX to REACH (Section 9.1.6.).

You have adapted the standard information requirement mentioned above according to Annex XI, Section 1.2 of REACH (weight of evidence).

In support of your adaptation, you have provided the following justification

Based on the presented sources of information, you argue that the available data gives sufficient information to conclude on the long-term aquatic toxicity to fish because:

i. the available chronic data in algae and daphnia reveal up to the water solubility of the substance in different media no toxic effects.;
ii. Potential short comings (analytics) in the algae test (OECD 201) were eliminated in a verification test with Lemna with accurate/elaborated analytics in the range of media solubility (see chapter 6.1.6).
iii. The nominal lowest toxicity with a LC 50 of 3,200 mg/L was derived in the acute fish study (OECD 203), being 32 times higher as the limit test concentration (WAF) in daphnia with EC50: >100 mg/L (OECD 202) or the concentration in the Lemna test, without having a toxic effect.

Overall, there is no indication that fish could be more sensitive towards the registered substance compared to daphnia and algae. There are enough data available for the Substance to omit further vertebrate testing.

We have assessed this information and identified the following issue(s):

As explained above, Annex XI, Section 1.2 states the conditions of using a weight of evidence adaptation. Furthermore, your weight of evidence adaptation lacks adequate and reliable documentation for integrating/weighing the lines of evidence provided for justifying data waiving (see **Appendix on Reasons common to several requests**).

Irrespective of the above mentioned deficiencies on the documentation, which in itself could lead to the rejection of the adaptation, ECHA has assessed the provided sources of information.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 9.1.6.1. at Annex IX includes similar information that is produced by the OECD TG 210 (ECHA Guidance R.7b, Section R.7.8.4.1). This includes investigating the following key elements:

1. Stage of embryonic development at the beginning of the test
2. Hatching of eggs and survival of embryos and larvae
3. Survival of juvenile fish
4. Abnormal appearance of larvae or juvenile fish
5. Abnormal behaviour (e.g. hyperventilation, uncoordinated swimming, atypical quiescence and atypical feeding behaviour)
6. Weight of the fish at the end of the test
7. Length of the fish at the end of the test

None of the sources of information you provided investigate these key elements. Therefore, they don’t provide information that would contribute to the conclusion on these key elements.

The sources of information (i) and (ii) do not investigate these key elements as the studies investigate different trophic levels other than fish: algae and aquatic plants (Lemna) and aquatic invertebrates.

The source of information (iii) related to the study submitted for short-term toxicity to fish, which was conducted according to a method that is applicable for investigating acute lethal toxicity to fish (ISO 7346-1), does not investigate the above key elements either. You have reported information on acute fish mortality without, for example, specifying the age of the test organisms. Therefore, you have failed to demonstrate that the results of this study are relevant to any of the key elements listed above.

Overall, as already explained under Section A.1, the Substance is poorly water soluble and information on short-term toxicity on fish and Daphnia is not valid.

Therefore, the provided justification does not contribute to the conclusion on these key elements.

Your weight of evidence adaptation does not include any relevant source of information to conclude on the property long-term toxicity to fish. Therefore your adaptation is rejected and information requirement is not fulfilled.

Study design

To fulfil the information requirement for the Substance, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (ECHA Guidance R.7.8.2.).

OECD TG 210 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix C.1.

Appendix D: Reasons to request information required under Annex X of REACH

1. Pre-natal developmental toxicity study 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.

ECHA understands that you submitted an adaptation according to Section 1 Annex XI, "*use of existing data, weight of evidence and read across approach*."

You have provided the following sources of information in rabbit/second species:

i. 2009 according to OECD TG 414 Prenatal developmental toxicity study via oral route with the Substance in rat;
ii. 1987 similar to OECD TG 414 via oral route with Diethylene glycol diethyl ether EC#203-963-7 in rabbit;
iii. 1986 similar to OECD TG 414 via oral route with Diethylene glycol diethyl ether EC#203-963-7 in mouse.

We have assessed this information and identified the following issue(s):

As explained under Appendix on Reasons common to several requests, the weight of evidence must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

As explained under Appendix on Reasons common to several requests, you have not included a justification for your weight of evidence adaptation for the information requirement, which would include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Irrespective of the above mentioned deficiency on the documentation, which in itself could lead to the rejection of the adaptation, ECHA has assessed the provided sources of information.

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 foreseen to be investigated in an OECD TG 414 study in a second species. The following aspects of this guideline include: 1) prenatal developmental toxicity in a second species, 2) maternal toxicity in a second species, and 3) maintenance of pregnancy in a second species.

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

While the sources of information (i - iii) provide relevant information on prenatal developmental toxicity, maternal toxicity and maintenance of pregnancy, sources of information have the following deficiencies affecting their reliability. However, only sources of information (ii - iii) provide relevant information in a second species.

First, the conditions of OECD TG 414 include having 20 female animals with implantation sites for each test and control group and exposure duration from implantation to the day prior to scheduled caesarean section. Study (ii) had duration of treatment during days 6-19 of gestation and the termination was on day 30 of gestation. Therefore, this study does not fulfil the conditions for exposure duration as foreseen in OECD TG 414.

Second, as explained in the Appendix on reasons common to several requests, the reported read-across approach does not fulfil the criteria in Annex XI, Section 1.5. Therefore, studies (ii - iii) cannot be used as part of weight of evidence adaptation according to Annex XI, Section 1.2.

Therefore, the sources of information (ii) and (iii) provide information on prenatal developmental toxicity, maternal toxicity and maintenance of pregnancy in a second species, but that information is not reliable.

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

Information on study design

A PNDT study according to the OECD TG 414 should be performed in the rabbit or rat as the preferred species. The test in the first species was carried out by using a rodent species (rat). Therefore, a PNDT study in a second species must be performed in the rabbit as preferred non-rodent species.

The study shall be performed with oral[4] administration of the Substance.

2. Extended one-generation reproductive toxicity study

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.

ECHA understands that you submitted a weight of evidence adaptation according to Annex XI , Section 1.2.

In support of your adaptation, you have provided the following sources of information:

i. 1990 similar to Two-Generation Reproduction Toxicity Study OECD TG 416 via oral route with analogue substance Diethylene Glycol Monoethyl Ether (DEGEE) EC#203-919-7 in mouse;
ii. 1985 non-TG study for one-generation reproductive toxicity study via oral route with Diethylene Glycol Monobutyl Ether EC#203-961-6 in rat;
iii. 1993 non-TG study for one-generation reproductive toxicity study via dermal route with diethylene glycol butyl ether EC#203-961-6 in rat.

We have assessed this information and identified the following issue(s):

As explained under Appendix on Reasons common to several requests, the weight of evidence must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

As explained under Appendix on Reasons common to several requests, you have not included a justification for your weight of evidence adaptation for the information requirement, which would include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

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

Irrespective of the above mentioned deficiency on the documentation, which in itself could lead to the rejection of the adaptation, ECHA has assessed the provided sources of information.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.7.3 at Annex X includes similar information that is produced by the OECD TG 443 design as specified in this decision. At general level, it includes information on the following key elements: 1) sexual function and fertility, 2) toxicity to offspring, 3) systemic toxicity and 4) if column 2 triggers are met, also information on sexual function and fertility of the offspring, toxicity of F2 offspring, developmental neurotoxicity and/or developmental immunotoxicity.

Sexual function and fertility

Sexual function and fertility on both sexes must cover information on mating, fertility, gestation (length), maintenance of pregnancy (abortions, total resorptions), parturition, lactation, organ weights and histopathology of reproductive organs and tissues, oestrous cyclicity, sperm count, sperm analysis, hormone levels, litter sizes, nursing performance and other potential aspects of sexual function and fertility.

a) The sources of information (i – iii) provide relevant information on sexual function and fertility, in particular, regarding functional fertility on males and females and investigations of reproductive organs.

However, the following deficiencies affect their reliability.

a) Functional fertility and histopathology of reproductive organs and tissues must be investigated in parental P0 animals as indicated in OECD TG 443 after at least ten weeks premating exposure duration if extension of Cohort 1B is not included to ensure the exposure of full spermatogenesis and folliculogenesis before mating. Substance specific justifications can support 10 week premaning exposure duration even if extension of Cohort 1B is included.

In the case of your Substance, the conditions to include the extension of Cohort 1B and to include 10 weeks premating exposure period are currently met (see below). The sources of information investigate sexual function and fertility with the premating exposure duration of six weeks in males and two weeks in females (ii) and no premating exposure period in P0 animals (iii).

Therefore, the condition above is not met.

b) With regard to the information from analogue substances, used as part of WoE, read-across adaptation can be used to adapt the standard information requirement, provided that the criteria in Annex XI, Section 1.5. are fulfilled. However, as explained in the Appendix on reasons common to several requests, the reported read-across approach does not fulfil the criteria in Annex XI, Section 1.5. Therefore, studies (i – iii) cannot be used as part of weight of evidence adaptation according to Annex XI, Section 1.2.

In the absence of reliable information on sexual function and fertility with sufficient premating exposure duration for both parental P0 animals, no conclusion can be drawn on sexual function and fertility as required by the information requirement.

Therefore, the condition above is not met.

Toxicity to offspring

Toxicity to offspring must cover information on deaths before, during or after birth, growth, external malformations, clinical signs, sexual maturity, oestrous cyclicity, histopathology of reproductive organs in adulthood and other potential aspects of toxicity to offspring.

The sources of information (i – iii) provide relevant information on the offspring, but have the following deficiencies affecting their reliability:

a) Under OECD TG 443, a study is to inform on toxicity to the offspring up to the adulthood, such as sexual maturity, oestrous cyclicity and histopathology of reproductive organs in adulthood.

Source of information (i) informs on toxicity to the offspring up to the adulthood, but sources of information (ii, iii) followed the offsprings until weaning. Therefore, source of information (i) covers sufficient duration of the study period but sources of information (ii, iii) do only partly.

Therefore, the condition above is not met.

b) The studies on analogue substances cannot be used as part of a weight of evidence adaptations for the reasons discussed above.

Therefore, the condition above is not met.

Systemic toxicity

Systemic toxicity must include information on clinical signs, survival, body weights, food consumption, haematology (full-scale), clinical chemistry (full-scale), organ weights and histopathology of non-reproductive organs (full-scale) and other potential aspects of systemic toxicity in the parental P and F1 generation up to adulthood.

The sources of information (i, ii) did not perform necropsy to F0 parental animals and therefore critical information such as haematology, clinical chemistry, organ weights and histopathology information is missing. The source of information (iii) provide only some relevant information on systemic toxicity as the animals were examined only for gross examinations without histopathology or clinical chemistry and haematology.

Therefore, the sources of information provide only partly relevant information on systemic toxicity.

The studies on analogue substances cannot, however, be used as part of a weight of evidence adaptations for the reasons discussed above.

In the absence of reliable information on toxicity to offspring up to the adulthood, no conclusion can be drawn on toxicity to offspring as required by the information requirement. Taken together, the relevant sources of information as indicated above, provide information on

- Sexual function and fertility on parental P0 generation but their reliability is significantly affected for the reasons provided above.
- Toxicity to offspring, but their reliability is significantly affected for the reasons provided above.
- Systemic toxicity, but only partly and their reliability is significantly affected for the reasons provided above.

Therefore, a significant amount of essential investigations are limited or totally lacking that would inform on sexual function and fertility, toxicity to offspring and systemic toxicity in order to conclude on these aspects.

Conclusion on the WoE adaptation

It is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 443 study with a design described in this decision. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

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 if there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA Guidance[1]. In this specific case ten weeks exposure duration is supported by the lipophilicity of the Substance (logKow = 6.94 at 25°C) to ensure that the steady state in parental animals has been reached before mating.

Therefore, the requested premating exposure duration is ten weeks.

In order to be compliant and not to be rejected due to too low dose levels, 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 must be included.

Extension of Cohort 1B

If the Column 2 conditions of 8.7.3., Annex X are met, Cohort 1B must be extended.

The extension is inter alia required, if the use of the registered substance is leading to significant exposure of consumers and professionals (column 2, first paragraph, lit. (a) of Section 8.7.3., Annex X) and if there are indications that the internal dose for the registered substance will reach a steady state in the test animals only after an extended exposure (column 2, first paragraph, lit. (b), second indent of Section 8.7.3., Annex X).

The use of the Substance is leading to significant exposure of consumers and professionals because the Substance is used by professionals as transfer of substance or mixture (charging and discharging) at non-dedicated and dedicated facilities (PROCs 8a, 8b) and by professionals and consumers as washing and cleaning products (PC 35), and by consumers as cosmetics and personal care products (PC 39).

In addition, there are indications that the internal dose for the Substance will reach a steady state in the test animals only after an extended exposure. Specifically, the $\log K_{ow}$ for the substance is above 4.5 indicating potential accumulation.

Therefore, Cohort 1B must be extended.

The F2 generation shall be followed to weaning allowing assessment of nursing and lactation of the F1 parents and postnatal development of F2 offspring. Investigations for F2 pups must be similar to those requested for F1 pups in OECD TG 443 and described in OECD GD 151[5]. It is recommended to aim at 20 litters per dose group.

Species and route selection

The study must be performed in rats with oral[6] administration.

Further expansion of the study design

No triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including Cohorts 2A and 2B 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[7].

[5] http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2013)10&doclanguage=en

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

[7] ECHA Guidance R.7a, Section R.7.6.

Appendix E: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

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

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

3. 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 on How to report robust study summaries[8].

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. Selection of the Test material(s)

   The Test Material used to generate the new data must be selected taking into account the following:
   - the variation in compositions reported by all members of the joint submission,
   - the boundary composition(s) of the Substance,
   - 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.

2. Information on the Test Material needed in the updated dossier
   - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[9].

[8] https://echa.europa.eu/practical-guides
[9] https://echa.europa.eu/manuals

Appendix F: Procedure

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

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 14 December 2020.

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

ECHA took into account your comments and amended the deadline.

In your comments on the draft decision, you requested an extension of the deadline to provide information from 24 to 36 months from the date of adoption of the decision. You provided a documentation from a laboratory, indicating that at least 32 months would be required to perform the PNDT and EOGRT studies. In addition you indicated that "The long-term aquatic toxicity studies will need an extensive investigation time to find a reliable long-term analytical method in an applicable test system for a hardly water-soluble substance".

On this basis, ECHA has extended 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 G: List of references - ECHA Guidance[10] and other supporting documents

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 where relevant.

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 where relevant.

Read-across assessment framework (RAAF, March 2017)[11]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[12]

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.

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.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[13]

[10] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[11] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[12] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[13] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

Appendix H: Addressees of this decision and their corresponding information requirements

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.