ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 26 August 2019

Addressee: [redacted]

Decision number: CCH-D-2114481209-44-01/F
Substance name: Bis(2-(2-butoxyethoxy)ethyl) adipate
EC number: 205-465-5
CAS number: 141-17-3
Registration number: [redacted]
Submission number: [redacted]
Submission date: 28/09/2017
Registered tonnage band: 100-1000

DECISION ON A COMPLIANCE CHECK

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

1. **Water solubility (Annex VII, Section 7.7.; test method: EU A.6./OECD TG 105) with the registered substance;**

2. **Skin sensitisation (Annex VII, Section 8.3.) with the registered substane**

   - **in vitro/in chemico skin sensitisation information on molecular interactions with skin proteins, inflammatory response in keratinocytes and activation of dendritic cells (Annex VII, Section 8.3.1.); and**

   - **in vivo skin sensitisation (Annex VII, Section 8.3.2.) in case the in vitro/in chemico test methods specified under point i) are not applicable for the substance or the results obtained are not adequate for classification and risk assessment;**

3. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. / OECD TG 471) with the registered substance;**

4. **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 registered substance;**

5. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance, provided that the studies requested under 3. and 4. have negative results;**

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

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

8. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

You have to submit the requested information in an updated registration dossier by ***7 March 2022***. You shall also update the chemical safety report, where relevant. The deadline has been set to allow for sequential testing.

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

Appeal

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

Authorised[1] by Ofelia Bercaru, Head of Unit, 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 1: Reasons

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation, where relevant.

0. General considerations for toxicological information

Your registration dossier contains for the endpoints addressed in this decision (points 2-8), adaptation arguments either in the form of predictions generated with the use of QSAR models under Annex XI, Section 1.3. and/or grouping and read-across approach under Annex XI, Section 1.5. to the REACH Regulation. ECHA has assessed your adaptation arguments in line with the conditions specified in Annex XI of the REACH Regulation:

QSAR models (Annex XI, Section 1.3.)

Your registration dossier contains QSAR predictions for endpoints:
- Skin sensitisation (Annex VII, Section 8.3.),
- In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.) and
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.).

For the use of QSAR models under Annex XI, Section 1.3., the following conditions shall be necessarily fulfilled:
- results are derived from a (Q)SAR model whose scientific validity has been established;
- the substance falls within the applicability domain of the model;
- results are adequate for the purpose of classification and labelling and/or risk assessment, and
- adequate and reliable documentation of the applied method is provided. Specifically, a QSAR Model Reporting Format (QMRF) and a QSAR Prediction Reporting Format (QPRF) are needed for ECHA to evaluate the adaptation.

ECHA has evaluated the provided QSAR information under each endpoint below.

Grouping of substances and read-across approach (Annex XI, Section 1.5.)

You have sought to adapt information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5, for the endpoints:
- Acute toxicity,
- Irritation/corrosion,
- Eye irritation,
- Skin sensitisation,
- Repeated dose toxicity,
- Genetic toxicity *in vitro*,
- Toxicity to reproduction, and
- Developmental toxicity.

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that

the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances[2]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus, physicochemical and degradation properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical and degradation properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[3]- (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

You consider to achieve compliance with the REACH information requirements for the registered substance Bis(2-(2-butoxyethoxy)ethyl) adipate (EC number 205-465-5) using data of structurally similar substances Dibutyl adipate, EC number 203-350-4; Bis(1-methylheptyl) adipate, EC number 203-601-8; Bis(2-ethylhexyl) adipate, EC number 203-090-1; Diisononyl Adipate, EC number 251-646-7; Diisodecyl adipate, EC number 248-299-9; Ditridecyl Adipate EC number 241-029-0 (hereafter the 'source substances').

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[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.
[3] Please see ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

You have provided documentation of the read-across adaptation, but the documentation that you provided in your dossier does not contain any specific justification whereby relevant human health properties of the registered substance may be predicted from data for the source substances. Specifically, your dossier does not address why such prediction would be possible.

With regard to the read-across hypothesis, you have not provided any details other than what is stated on the cover page of your read-across justification document: "*Read-across rationale Category approach: different compounds having quantitatively similar properties. Variations in the properties observed among the source substances. Prediction based on a regular pattern or on a worst-case approach.*"

According to the ECHA Guidance on information requirements and chemical safety assessment Chapter R.6.2, Section R.6.2.4.1, (version 1.0, May 2008) a category hypothesis should address "*the set of inclusion and/or exclusion rules that identify the ranges of values within which reliable estimations can be made for category members for the given endpoint. These rules, can be described as the applicability domain for an endpoint and provide a means of extending the category membership to chemicals not explicitly included in the current definition of a category.*" Furthermore, according to the ECHA Guidance on information requirements and chemical safety assessment Chapter R.6.2, Section R.6.2.2.2, (version 1.0, May 2008) "*a demonstration of consistent trends in the behaviour of a group of chemicals is one of the desirable attributes of a chemical category and one of the indicators that a common mechanism for all chemicals is involved*". Finally, Annex XI, Section 1.5 requires that in all cases where read-across is used that adequate and reliable documentation of the applied method is provided.

For all categories you must clearly and unambigiously define the applicability domain within which you make reliable predictions. This is done by defining a set of inclusion and exclusion criteria. ECHA considers read-across to be endpoint specific. This means that you must explain in detail why a specific information requirement for your target substance can be accurately predicted from the available data on your source substances. You must also explain how you make this prediction and demonstrate that all relevant available data on the source substances, within the defined group, has been taken into account. In order to allow an independent assessment of the prediction all studies (for each endpoint where read-across is used) must be documented to such a detail that allows such an assessment. You have not provided any of the above mentioned information. In the absence of this information, ECHA cannot verify that the properties of the registered substance can be predicted from the data on the source substance.

Further to this, a robust study summary is required under Article 10(a)(vii), and ECHA considers that the information provided in the endpoint study record does not meet the requirements of a robust study summary, as defined in Article 3(28). ECHA has provided a practical guide for "How to report robust study summaries". ECHA considers there is not sufficient information to make an independent assessment of the study minimising the need to consult the full study report, because you have not provided robust study summaries for your source studies. You have provided endpoint study records in IUCLID labelled as 'read-across'; however, these endpoint study records are virtually empty (generally only the fields "test material" and "Interpretation of results" are filled in) and therefore, the endpoint records do not contain the information needed for an independent assessment of how the study was conducted nor its results. Accordingly ECHA considers that for the above mentioned endpoints, you have failed to meet the requirement of Annex XI, 1.5, that adequate and reliable documentation of the applied method shall be provided.

In the absence of a read-across hypothesis and adequate and reliable documentation of the applied method, ECHA cannot verify that the properties of the registered substance can be predicted from the data on the source substance.

Hence, you have not established that relevant properties of the registered substance can be predicted from data on the registered substance. Since your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5., it is rejected and it is necessary to perform testing on the registered substance.

PHYSICOCHEMICAL PROPERTIES OF THE SUBSTANCE

1. Water solubility (Annex VII, Section 7.7.)

"Water solubility" is a standard information requirement as laid down in Annex VII, Section 7.7 of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

As a key study you have provided an endpoint study record, which you indicate to be an experimental study. The provided study is a value from a handbook (Plasticizer Databook, author Anna Wypych, Chemtec Publishing, 2013). You conclude that the test item is not soluble in water.

According to ECHA Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7a (version 6.0, July 2017), Section R.7.1.1.3, information from secondary sources (e.g. handbook data) can be used in accordance with limitations described in the same Guidance for each endpoint, and within the constraints of Annex XI to REACH. Specifically for physical-chemical properties, Section 1.1.1. of Annex XI states, that existing data can be considered to be equivalent to data generated with the test methods referred to Article 13(3) if the following conditions, among others, are met:

1. Sufficient documentation is provided to assess the adequacy of the study;
2. The study results are adequate for the purpose of classification and labelling and/or risk assessment;

ECHA notes that you have not provided any documentation of the study, other than the final result. Therefore, ECHA cannot assess the validity of the study or the reported value. As a consequence, the reported result is not considered to be adequate for the purpose of classification and labelling and/or risk assessment.

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

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Water solubility (test method: EU A.6./OECD TG 105)

Guidance for determining appropriate test methods for the water solubility is available in the ECHA Guidance on information requirements and chemical safety assessment (version 6.0, July 2017), Chapter R.7a.

Notes for your consideration

ECHA notes that in your dossier you have reported the result of 35.55 mN/m for surface tension indicating that the substance is surface active. For such substances the estimation of water solubility alone can lead to uncertain results and hence also the critical micelle concentration (the maximum concentration of the freely solubilised surfactant in water) should be determined as advised in ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017) and the OECD Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23.

2. Skin sensitisation (Annex VII, Section 8.3.)

Skin sensitisation is a standard information requirement in Annex VII, Section 8.3. to the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement. Column 1 of Section 8.3. requires the registrants to submit information allowing a conclusion whether the substance is a skin sensitiser and whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A), and risk assessment, where required.

You have sought to adapt this information requirement according to Annex XI, Section 1.3 criteria using the QSAR approach, and Annex XI, Section 1.5. read-across approach, of the REACH Regulation by providing the following information:

a. QSAR approach on different tools (Toxtree and Vega), rated with reliability of 2 (reliable with restrictions) with the registered substance. The prediction was considered to be positive i.e. sensitising. You also state that the substance is not completely falling into the applicability domain.
b. Experimental studies according to non-LLNA *in vivo(s)* method using analogue substances. In the endpoint study record you only state "*Available data indicate that category members are not sensitizing.*". In the read-across justification document, attached into the dossier, you refer to experimental studies on dibutyl adipate, and Bis(2-ethylhexyl) adipate, where only limited information on the studies have been provided and hence the quality of those studies cannot be confirmed, as explained in Section 0 above.
c. Statement "*the study does not need to be conducted because adequate information is available from the category read-across approch adopted.*".

ECHA has evaluated the provided information and notes the following:

- Concerning the use of the QSAR adaptation, the provided QSAR prediction is not acceptable, because you have not provided any documentation, i.e. a QMRF and a QPRF, for the prediction. Therefore, ECHA cannot establish whether the model is scientifically valid, whether the registered substance falls within the applicability domain of the model, and whether the results are adequate for classification and labelling and/or risk assessment.;
- You have not provided any considerations of the outcome of the prediction (sensitising) and how that links to the statements that you have provided from the category approach where *in vivo* data has been considered. In addition, you state in the read-across justification document, that the predicted values have been confirmed, although differing outcomes were obtained i.e. positive QSAR prediction and negative *in vivo* skin sensitisation study on an analogue substance.
- Concerning the read-across approach, as explained in Appendix 1, Section 0 of this

decision your adaptation of the information requirement is rejected.

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

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information on skin sensitisation derived with the registered substance subject to the present decision:

a. *in vitro/in chemico* information on molecular interactions with skin proteins, inflammatory response in keratinocytes and activation of dendritic cells (Annex VII, Section 8.3.1); and
b. local lymph node assay (Annex VII, Section 8.3.2; test method: EU B.42./OECD 429) with the registered substance only in case the *in vitro/in chemico* test methods specified under point a) are not applicable for the substance or the results obtained are not adequate for classification and risk assessment.

ECHA informs you that the Lead registrant of your Joint submission [redacted] has already been requested in a decision to provide some of the same information from experimental studies involving vertebrate animals. In accordance with Title III of the REACH Regulation, namely the obligations to share available information of studies on vertebrate animals, you shall not perform new testing involving vertebrate animals in order to comply with the present decision where such data is already available. Under these provisions you are compelled to request this information from other registrants of the same substance. All the registrants concerned shall make every effort to reach an agreement on the fair, transparent and non-discriminatory sharing of the cost. In addition, you are reminded of the obligations imposed by Articles 11 of the REACH Regulation on all the registrants of the same substance to submit registrations for the same substance jointly.

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

An "In vitro gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In your registration dossier you have provided the following information;

a. Experimental study [redacted] 2001), supporting study rated reliability 2. OECD TG 471, Ames test with the registered substance, negative with and without S9.

To fulfil the information requirement, a robust study summary is required under Article 10(a)(vii). ECHA considers that the information provided for this study record does not meet the requirements of a robust study summary[4], as defined in Article 3(28), for the reasons as set out below.

The OECD TG 471 test was performed with 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537) and one strain of *E. coli* WP2 uvrA. In the study record you

[4] ECHA's practical guide for "*How to report robust study summaries*", available at: https://echa.europa.eu/practical-guides

indicated that for all the strains tested the results were negative, with and without metabolic activation. However, the experimental study you provided in the dossier does not contain sufficient reporting details because study design and results details, including information on the choice of test concentrations, the number of doses evaluated, data on the number of revertant colonies per plate for the treated doses and the controls, and a negative control with a number of revertant colonies per plate inside the historical control range of the laboratory are missing. Therefore, the quality and validity of the study cannot be confirmed and there is not sufficient information to make an independent assessment of the study, as required by Article 3(28).

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

ECHA considers that the bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. of the REACH Regulation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit following information derived with the registered substance subject to the present decision: Bacterial reverse mutation test (test method: EUB.13/14. / OECD TG 471).

4. 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 as laid down in Annex VIII, Section 8.4.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In your registration dossier you have provided the following:

a. Experimental study ([redacted] 2001), supporting study rated reliability 2. OECD TG 473 with the registered substance, negative with and without S9.
b. Three QSAR predictions using ACD/Percepta, Leadscope, VEGA model for mouse lymphoma and chromosome aberrations submitted as supporting information rated KL2. All prediction results are negative.
c. Statement *"According to the category read-across approach, no genotoxic potential is expected for the adipic acid diesters category."*

However, the experimental study provided is not sufficient to address the endpoint for the following reason:

- The experimental study (a) provided on the registered substance does not contain sufficient reporting details such as study design details, therefore the quality and validity of the study cannot be confirmed.

Regarding the use of QSAR approach, the provided QSAR predictions are not acceptable i.e. meeting the Annex XI, Section 1.3 criteria, for the following reasons:

- You have not provided any documentation, i.e. a QMRF and a QPRF, for the prediction. Therefore, ECHA cannot establish whether the model is scientifically valid,

whether the registered substance falls within the applicability domain of the model, and whether the results are adequate for classification and labelling and/or risk assessment;
- You have not provided any considerations of the outcome of the prediction and how that links to the statements that you have provided from the category approach where *in vivo* data has been considered.

Regarding the read-across approach, as explained in Appendix 1, Section 0 above, your adaptation according to Annex XI, Section 1.5. is rejected.

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

ECHA considers that the *in vitro* mammalian chromosome aberration test (test method OECD TG 473) and the *in vitro* mammalian cell micronucleus test (OECD TG 487) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.2. of the REACH Regulation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian chromosome aberration test (test method: OECD TG 473) or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487).

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

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained.

Currently your dossier does not have acceptable information on the two information requirements mentioned above under points 3 and 4. Adequate information on *in vitro* gene mutation in mammalian cells will however need to be present in the technical dossier for the registered substance to meet this information requirement provided that both studies requested under 3 and 4 have negative results.

You have provided a waiving argument for this endpoint: "*The available information deriving from QSAR and read-across approaches, is sufficient to assess the hazard of bis[2-(2-butoxyethoxy)ethyl] adipate, and no further testing is deemed necessary.*"

Regarding the provided QSAR prediction, it is not acceptable, because you have not provided any documentation, i.e. a QMRF and a QPRF, for the prediction. Therefore, ECHA cannot establish whether the model is scientifically valid, whether the registered substance falls within the applicability domain of the model, and whether the results are adequate for classification and labelling and/or risk assessment.

Regarding the read-across approach, as explained above in Appendix 1, Section 0 of this present decision, your adaptations of the information requirement is rejected. Therefore your waiving argument cannot be accepted.

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

ECHA considers that the *in vitro* mammalian cell gene mutation tests using the *Hprt* and *xprt* genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490) provided that the studies requested under 3 and 4 give negative results. ECHA set the deadline for provision of the information to allow for sequential testing.

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

"Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. No such evidence is presented in the dossier. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier under this endpoint you have provided the following information:

a. Three QSAR predictions providing supporting information, rated reliability 2. All predictions were negative and predictions considered reliable by registrant.
b. Read-across from source substance for a one-generation reproduction study in rats. No reliability rating and only the following information is provided: *"NOAEL for fertility was 1000 mg/kg bw/d (highest dose level tested). As for developmental effects the oral NOAEL was established at 500 mg/kg bw/d. The only effect observed at the next higher dose level tested was reduced body weight gain of the pups. DEGBE caused no teratogenic effects after oral administration. No effects were observed in a dermal one-generation study at doses up to 2000 mg/kg bw/d (EU RAR)"*
c. Statement *"According to the category approach, no effects on reproduction are expected for adipic acid diesters category members. However, the worst case NOAEL available among category members is used for risk assessment purposes."*

You have sought to adapt this information requirement according to Annex XI, Section 1.3 criteria for the QSAR approach and Annex XI Section 1.5., concerning grouping and read-across approach of the REACH Regulation.

Regarding the provided QSAR predictions, they are not acceptable, because you have not provided any documentation, i.e. a QMRF and a QPRF, for the prediction. Therefore, ECHA cannot establish whether the model is scientifically valid, whether the registered substance falls within the applicability domain of the model, and whether the results are adequate for classification and labelling and/or risk assessment. Therefore, your adaptation according Annex XI Section 1.3. is rejected.

Concerning the proposed adaptation for a one-generation study, ECHA notes that the quality of study cannot be assessed, because you have not provided any documentation of the study. Further, as explained in Appendix 1, Section 0 of this present decision, your adaptation according to Annex XI, Section 1.5. is rejected.

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

According to the test methods OECD TG 421/422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with rats.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

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

Notes for your considerations

For the selection of the appropriate test, please consult ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.5 and 7.6 (version 6.0, July 2017). You should also carefully consider the order of testing of the requested screening (OECD TG 421/422) and the developmental toxicity studies (OECD TG 414) to ensure that unnecessary animal testing is avoided, paying particular attention to the endpoint specific guidance (https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf).

7. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have provided a waiving argument for this endpoint: *"a sub-chronic toxicity study (90 days) by the oral route does not need to be conducted because adequate data are available from the category read-across approach."*

Regarding the read-across approach, as explained above in Appendix 1, Section 0 of this decision, your adaptation of the information requirement is rejected.

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

ECHA has evaluated the most appropriate route of administration for the study based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 5.0, December 2016) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance is a liquid of very low vapour pressure and no uses with spray application are reported that could potentially lead to aerosols of inhalable size. Hence, the test shall be performed by the oral route using the test method OECD TG 408.

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

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

Please note that a decision requesting this study has also been sent to the other Registrant(s) of this substance. According to Article 53 of the REACH Regulation you will need to agree with the Registrant(s) of this substance on who will perform the test.

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

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

You have provided a waiving argument for this endpoint: *"No other experimental data are considered necessary to assess the hazard of the substance, since the available information derived from read-across and QSAR approaches is considered sufficient."*

ECHA notes that you have not reported any QSAR predictions for this endpoint. Furthermore, ECHA is currently not aware of any scientifically valid QSAR models that could reliably predict the outcome of experimental tests for this endpoint and for the registered substance.

Regarding the read-across approach, as explained above in Appendix 1, Section 0 of the present decision, your adaptation of the information requirement is rejected.

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

According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

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

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 20/07/2018.

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

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

In your comments you stated that you have received the draft decision and that you do not have "specific questions." ECHA took your comments into account and did not amend the request(s).

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

ECHA received proposals for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendments.

ECHA referred the draft decision to the Member State Committee.

You did not provide any comments on the proposed amendment(s).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-65 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

2. Failure to comply with the requests in this decision will result in a notification to the enforcement authorities of your Member State.

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

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

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