Helsinki, 21 August 2018

Addressee: [redacted]

Decision number: CCH-D-2114440485-49-01/F
Substance name: Bis(2-ethylhexyl) cyclohexane-1,4-dicarboxylate
EC number: 283-829-2
CAS number: 84731-70-4
Registration number: [redacted]
Submission number: [redacted]
Submission date: 24/10/2017
Registered tonnage band: Over 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. **Robust study summary for Two-generation reproductive toxicity study with the registered substance (Annex X, Section 8.7.3. in conjunction with Annex I, Section 1.1.4.);**

2. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rabbit), oral route with the registered substance;**

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

4. **Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210) with the registered substance;**

5. **Robust study summary for the bioaccumulation in aquatic species study reported in the registration dossier (Annex IX, Section 9.3.2. in conjuction with Annex I, Section 3.1.5.);**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH Regulation. To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by ***28 August 2019***. You also have to update the chemical safety report, where relevant.

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

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 Kevin Pollard, Head of Unit, Evaluation E1

[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.

ECHA
EUROPEAN CHEMICALS AGENCY

Appendix 1: Reasons

TOXICOLOGICAL INFORMATION

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

1. **Robust study summary for Two-generation reproductive toxicity study (Annex X, Section 8.7.3. in conjunction with Annex I, Section 1.1.4.);**

Pursuant to Article 10(a)(vii) of the REACH Regulation, the information set out in Annex VII to XI must be provided in the form of a robust study summary if required under Annex I. Article 3(28) defines a robust study summary as a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study minimising the need to consult the full study report. Guidance on the preparation of the robust study summaries is provided in the Practical Guide 3 on "How to report robust study summaries" (version 2.0, November 2012).

An Extened one-generation reproductive toxicity study is a standard information requirement as laid down in Annex IX, Section 8.7.3. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have submitted a testing proposal for an extended one-generation reproductive toxicity study. As part of your alternative method consideration, you state that there is an ongoing two-generation reproductive toxicity study with the registered substance that will be finalised in October 2018. You also state that the study is commenced after 13 March 2015 because it is necessary to fulfil the regulatory requirements in jurisdiction outside of the EU that do not currently accept the extended one-generation reproductive toxicity study as part of its information requirement. In addition, you make reference to *"ECHA Guidance on Information Requirements and Chemical Saftey Assessment Chapter R.7a: Endpoint specific guidance, Version 6.0, July 2017, section R.7.6.4.2.4"* and state that *"Although the two-generation reproductive toxicity study may lack information on some parameters which are part of EU B.56 (OECD TG 443), it addresses the fertility endpoint in two-generations and is adequate for risk assessment and classification and labeling, including categorization when conducted according to the EU B.35 (OECD TG 416)"*. Furthermore, you state that the available information do not support to trigger developmental neurotoxicity and developmental immunotoxicity. Finally, you conclude that *"While a new Two Generation toxicity study cannot be proposed to meet REACH Annex X, 8.7.3, in that a Two-generation reproductive study is already ongoing, and the substance does not trigger any concerns for developmental neurotoxicity and/or developmental immunotoxicity, the data already being generated is considered sufficient to address the REACH Annex X, 8.7.3 endpoint. Therefore it is not considered justifiable or ethical to perform additional studies for this endpoint"*.

ECHA considers the provided information and consequently terminated the testing proposal examination for the extended one-generation reproductive toxicity study, as communicated to you on 18 January 2018 (communication number: TPE-C-2114387387-33-01/F).

Currently, your registration dossier is non-compliant as you have not submited information to meet the information requirement according to Annex X, Section 8.7.3. ECHA understands that your intention is to submit results of the two-generation reproductive toxicity study with the registered substance once the study is finalised. In this regard, you are required to provide suffient documentation of the study result in accordance to Article 3(28) of the REACH Regulation for independent assessment of the adequacy of the study and its use for hazard assessment. Furthermore, pursuant to Article 10 (a)(vii) and Annex I, Section 1.1.4. if there are studies addressing effect on reproduction, then, having taken into account possible variables (e.g. conduct, adequacy, relevance of test species, quality of results, etc.), normally the study or studies giving rise to the highest concern shall be used to establish the DNELs and a robust study summary shall be prepared for that study or studies and included as part of the technical dossier. Robust summaries will be required of all key data used in the hazard assessment.

ECHA notes that in your comments on the draft decision you have agreed to provide enhanced robust study summary for the two-generation reproductive toxicity study with the registered substance in the updated registration dossier.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information: Robust study summary for the two-generation reproductive toxicity study with the registered substance.

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

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The technical dossier contains information on a pre-natal developmental toxicity study in rats by the oral route using the registered substance as test material.

However, there is no information provided for a pre-natal developmental toxicity study in a second species. Instead, you have provided the following justification: "*According to Regulation (EC) No. 1907/2006, Annex IX, Section 8.7.2, column 2: the pre-natal developmental toxicity studyshall be initially performed on one species. A decision on the need to perform a study on a second species should be based on the outcome of the first test and all other relevant available data. For this substance, there are one reproductive/developmental screening study and one pre-natal developmental study in rats available which shows no reproductive or developmental toxicity. Therefore, from hazard considerations, the developmental toxicity study on the second species is not necessary*".

ECHA understands that you have sought to adapt the information requirement according to REACH Annex IX, Section 8.7.2., column 2. However, your justification is applicable for the information requirement of substance registered at 100 tonnes or more and currently your substance is registered at 1000 tonnes or more. As indicated above, pre-natal developmental toxicity study on second species is a standard information requirement at REACH Annex X level. Availability of information on two species allows a more comprehensive evaluation of pre-natal developmental toxicity.

The information available currently, including the submitted pre-natal developmental toxicity study in the first species, do not support adaptations according to REACH Annex X, Section 8.7., column 2 or Annex XI.

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

The test in the first species was carried out by using a rodent species (rat). According to the test method EU B.31./OECD 414, the rabbit is the preferred non-rodent species. On the basis of this default assumption, ECHA considers that the test should be performed with rabbit as a second 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.

ECHA notes that in your comments on the draft decision you have agreed to perform requested Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a second species (rabbit) 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: EU B.31./OECD TG 414) in a second species (rabbit) by the oral route.

Notes for your consideration
ECHA notes that a revised version of OECD TG 414 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. You should test in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

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

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

You have sought to adapt this information requirement according to Annex IX, Section 9.1.5., column 2. You provided the following justification for the adaptation: "*According to Regulation (EC) No. 1907/2006, Annex IX, section 9.1, column 2, Long-term toxicity testing shall be proposed by the registrant if the chemical safety assessment according to Annex I indicates the need to investigate further the effects on aquatic organisms. Ready Biodegradability test shows 54.1% degradation after 28 days, which does not fulfil the minimum criteria set out by the OECD method. This does however indicate T½ was achieved within 28 days, highlighting the materials propensity for biodegradation. An inherent biodegradability test shows 80.5% degradation after 28 days, therefore it is considered that the material is inherently biodegradable and as such not persistent in environmentally significant conditions. While the Log Kow was shown to be 8.84, a bioaccumulation study has shown the mean BCF to be 9. The substance was shown not to significantly accumulate in fish tissue and was observed to be eliminated from the fish tissues over a 25 day depuration period. Based on this information the biological half-life of the test item is considered to be between 6 to 25 days.*

In toxicity tests, the substance also displayed no observable effect on fish, daphnia, algae and microorganisms at the nominal concentration of 100mg/L. As such the material would not be considered toxic. The above information gives rise to predicted no effect concentrations which are undemanding and as such the chemical safety assessment should conclude safe use of the material. With this in mind, further testing on the substance is considered not necessary."

ECHA notes that based on information provided in the registration dossier the substance is poorly water soluble (WS <1mg/l). Thus, ECHA considers that short-term toxicity test with aquatic invertebrates is not sufficient for the substance as the lack of toxicity to enable estimation of relevant effect concentration in the short-term test cannot exclude long-term toxicity (48h EC50 above 0.17 mg/l is reported in the registation dossier for *Daphnia magna*, however some toxicity, as reported in the dossier, was observed in the short-term test: "*5% of immobilization and 45% of lethargic symptoms (erratic swimmng) were observed at the end of the test in the nominal concentration of 100 mg/L WAFs (mean measured concentration: 0.17 mg/L"*).

ECHA notes that poorly water soluble and/or hydrophobic substances require longer time to be significantly taken up by the test organisms and so steady state conditions are likely not to be reached within the duration of a short-term toxicity test. For this reason, short-term tests may not give a true measure of toxicity for hydrophobic/poorly water soluble substances and toxicity may actually not even occur at the water solubility limit of the substance if the test duration is too short. Still, long-term toxicity cannot be excluded and should be investigated. Annex VIII 9.1.3. and Annex VII 9.1.1. of the REACH Regulation explicitly recommend that long-term aquatic toxicity tests be considered if the substance is poorly water soluble.

Furthermore, for the purpose of the Chemical Safety Assessment (CSA), the information under REACH should at least cover species from three trophic levels: algae/aquatic plants, invertebrates (Daphnia preferred), and fish (as mentioned in Guidance Chapter R7b, version 2017). As explained above, there is no adequate aquatic invertebrates toxicity data available, which is necessary for the CSA purposes.

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

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

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) *Daphnia magna* reproduction test (test method EU C.20. / OECD TG 211) is the preferred test to cover the standard information requirement of Annex IX, Section 9.1.5.

ECHA notes that in your comments on the draft decision you have agreed to provide results of the recently performed *Daphnia magna* reproduction test (test method: EU C.20./OECD TG 211) with the registered substance in the updated registration dossier.
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: *Daphnia magna* reproduction test (test method: EU C.20./OECD TG 211).

Notes for your consideration

Once results of the test on long-term toxicity to aquatic invertebrates are available, you shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation.

Due to the low solubility of the substance in water you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity tests and for calculation and expression of the result of the tests.

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

"Long-term toxicity testing on fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. of the REACH Regulation. Adequate information on Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.), or Fish, short-term toxicity test on embryo and sac-fry stages (Annex IX, 9.1.6.2.), or Fish, juvenile growth test (Annex IX, 9.1.6.3.) needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex IX, Section 9.1.6., column 2. You provided the following justification for the adaptation: *"According to Regulation (EC) No. 1907/2006, Annex IX, section 9.1 column 2, Long-term toxicity testing shall be proposed by the registrant if the chemical safety assessment according to Annex I indicates the need to investigate further the effects on aquatic organisms. Ready Biodegradability test shows 54.1% degradation after 28 days, which does not fulfil the minimum criteria set out by the OECD method. This does however indicate T½ was achieved within 28 days, highlighting the materials propensity for biodegradation. An inherent biodegradability test shows 80.5% degradation after 28 days, therefore it is considered that the material is inherently biodegradable and as such not persistent in environmentally significant conditions. While the Log Kow was shown to be 8.84, a bioaccumulation study has shown the mean BCF to be 9. The substance was shown not to significantly accumulate in fish tissue and was observed to be eliminated from the fish tissues over a 25 day*

depuration period. Based on this information the biological half-life of the test item is considered to be between 6 to 25 days. In toxicity tests, the substance also displayed no observable effect on fish, daphnia, algae and microorganisms at the nominal concentration of 100mg/L. As such the material would not be considered toxic. The above information gives rise to predicted no effect concentrations which are undemanding and as such the chemical safety assessment should conclude safe use of the material. With this in mind, further testing on the substance is considered not necessary."

ECHA notes that based on information provided in the registration dossier the substance is poorly water soluble (WS <1mg/l). Thus, ECHA considers that short-term toxicity test with fish is not sufficient for the substance as the lack of toxicity in the short-term test (96h LC50 above 0.05 and above 0.35 mg/l are reported in the registation dossier for fish in key and supporting studies, respectively) cannot exclude long-term toxicity.

ECHA notes that poorly water soluble and/or hydrophobic substances require longer time to be significantly taken up by the test organisms and so steady state conditions are likely not to be reached within the duration of a short-term toxicity test. For this reason, short-term tests may not give a true measure of toxicity for hydrophobic/poorly water soluble substances and toxicity may actually not even occur at the water solubility limit of the substance if the test duration is too short. Still, long-term toxicity cannot be excluded and should be investigated. Annex VIII 9.1.3. and Annex VII 9.1.1. of the REACH Regulation explicitly recommend that long-term aquatic toxicity tests be considered if the substance is poorly water soluble.

Furthermore, for the purpose of the Chemical Safety Assessment (CSA), the information under REACH should at least cover species from three trophic levels: algae/aquatic plants, invertebrates (Daphnia preferred), and fish (as mentioned in Guidance Chapter R7b, version 2017). As explained above, there is no adequate fish toxicity data available, which is necessary for the CSA purposes. Therefore, your adaptation of the information requirement cannot be accepted.

ECHA further notes that due to lack of effects in short-term studies it is not possible to determine the sensitivity of species. Therefore, the Integrated testing strategy (ITS) outlined in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b (Section R.7.8.5 including Figure R.7.8-4), is not applicable in this case and the long-term studies on both invertebrates and fish are necessary to be conducted.

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

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) fish early-life stage (FELS) toxicity test (test method OECD TG 210), fish short-term toxicity test on embryo and sac-fry stages (test method EU C.15. / OECD TG 212) and fish juvenile growth test (test method EU C.14. / OECD TG 215) can be performed to cover the standard information requirement of Annex IX, Section 9.1.6.

However, the FELS toxicity test according to OECD TG 210 is more sensitive than the fish, short-term toxicity test on embryo and sac-fry stages (test method EU C.15 / OECD TG 212), or the fish, juvenile growth test (test method EU C.14. / OECD TG 215), as it covers

several life stages of the fish from the newly fertilized egg, through hatch to early stages of growth (see ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), *Chapter R7b, Section R.7.8.4.1.*

Moreover, the FELS toxicity test is preferable for examining the potential toxic effects of substances which are expected to cause effects over a longer exposure period, or which require a longer exposure period of time to reach steady state (ECHA *Guidance Chapter R7b,* version 4.0, June 2017).

ECHA notes that in your comments on the draft decision you have proposed to include in the registration dossier results of the study performed according to OECD TG 215 instead of requested study according to OECD TG 210. According to the ECHA's Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7b (version 4.0, June 2017) OECD TG 215 is "*shorter and less expensive option to the FELS test for substances of log Kow<5*". However, ECHA notes that according to the information provided in the registration dossier experimentaly determined log Kow (logarithmic octanol-water partitioning coefficient) of the substance is above 6. Therefore, ECHA considers that due to the high log Kow testing according to the OECD TG 215 is not relevant and not acceptable for the registered substance.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Fish, early-life stage (FELS) toxicity test (test method: OECD TG 210).

Notes for your consideration

Once results of the test on long-term toxicity to fish are available, you shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation.

Due to the low solubility of the substance in water you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity tests and for calculation and expression of the result of the tests.

5. Robust study summary for the bioaccumulation in aquatic species study reported in the registration dossier (Annex IX, Section 9.3.2. in conjuction with Annex I, Section 3.1.5.)

Pursuant to Article 10(a)(vii) of the REACH Regulation, the information set out in Annex VII to XI must be provided in the form of a robust study summary if required under Annex I. Guidance on the preparation of the robust study summaries is provided in the Practical Guide 3 on "How to report robust study summaries" (version 2.0, November 2012).

A "Bioaccumulation in aquatic species, preferably fish" is a standard information requirement as laid down in Annex IX, Section 9.3.2. 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. Furthermore, pursuant to Article 10 (a)(vii) and Annex I, Section 3.1.5., where there is more than one study addressing the same effect, then the study or studies giving rise to the highest concern shall be used to draw a

conclusion and a robust study summary shall be prepared for that study or studies and included as part of the technical dossier. Robust summaries will be required of all key data used in the hazard assessment.

You have provided a study record for a [redacted] to meet the standard information requirement of Annex IX, Section 9.3.2.

However, ECHA notes that, the documentation of this study is insufficient and does not allow an independent assessment of the adequacy of this study, its results and its use for hazard assessment, as required by Art. 3(28) Of the REACH Regulation. In particular, the following elements are not clear: higher end of recovered nominal test concentration (either 108% or 190% of the nominal concentration); whether or not kinetic parameters were dependant on test concentration; whether time-weighted average concentration of the substance in water was used for estimation of BCF at steady state. Therefore, you need to provide a complete robust study summary with the above missing elements for this study.

Hence, 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 notes that in your comments on the draft decision you have agreed to provide enhanced robust study summary for the bioaccumulation in aquatic species study with the registered substance in the updated registration dossier.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information: Robust study summary for the for the bioaccumulation in aquatic species study reported in the registration dossier (Annex IX, Section 9.3.2. in conjuction with Annex I, Section 3.1.5.).

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 1 February 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 agreed to the draft decision. ECHA took your comments into account and did not amend the requests.

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

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

Appendix 3: Further information, observations and technical guidance

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

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

3. In carrying out the tests required by the present decision, it is important to ensure that the particular sample of substance tested 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. If the registration of the substance covers different grades, the sample used for the new tests must be suitable to assess these.

   Furthermore, 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.