EUROPEAN CHEMICALS AGENCY

Helsinki, 25 July 2017

Addressee: [redacted]

Decision number: CCH-D-2114367241-55-01/F
Substance name: BIS(2-ETHYLHEXYL) FUMARATE
EC number: 205-448-2
CAS number: 141-02-6
Registration number: [redacted]
Submission number: [redacted]
Submission date: 29.03.2016
Registered tonnage band: 1000+T

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

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

3. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce some toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;**

4. **Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: Algae growth inhibition test, EU C.3./OECD TG 201) with the registered substance;**

5. **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;**

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 **3 February 2020**. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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

Appeal

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

Authorised[1] by 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.

Appendix 1: Reasons

TOXICOLOGICAL INFORMATION

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

Grouping of substances and read-across approach for toxicological information

In your comments on the draft decision according to Article 50(1) of the REACH Regulation, you have sought to adapt the information requirements for the pre-natal developmental toxicity study in a first species (Annex IX, Section 8.7.2.), the pre-natal developmental toxicity in a second species (Annex X, Section 8.7.2.), and the extended one-generation reproductive toxicicty study (Annex X, Section 8.7.3.) by applying a read-across approach in accordance with Annex XI, Section 1.5.

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 the structural similarities and differences of the source and registered substances. 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 property and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the property under consideration. Certain physicochemical properties determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms in bioaccumulation and toxicity tests. Thus, physicochemical properties influence the human health and environmental properties of a substance and must therefore be considered in read-across assessments. However, the information on physicochemical properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the property under consideration.

The ECHA Read-across assessment framework foresees in line with Annex XI Section 1.5. that there are two options which may form the basis of a read-across hypothesis[2]- (1) "(Bio)transformation to common products" and (2) "Different compounds have the same type of effect(s)".

Finally, Annex XI, Section 1.5. lists four additional requirements, which deal with the quality of the studies used in the read-across.

a) Description of the grouping and read-across approach

You seek to adapt the information requirements for a pre-natal developmental toxicity in a first species (Annex IX, Section 8.7.2.), a pre-natal developmental toxicity in a second species (Annex X, Section 8.7.2.), and an extended one-generation reproductive toxicicty study (Annex X, Section 8.7.3.) by applying a read-across approach according to Annex XI, Section 1.5.

You consider to achieve compliance with the REACH information requirements for the registered substance bis(2-ethylhexyl)fumarate (also referred to as dioctylfumarate or DOF) using data of the following structurally similar substances (hereafter the 'source substances'):

- dibutylfumarate (DBF; CAS No 105-75-9)
- 2-ethylhexan-1-ol
- fumaric acid

You have provided read-across documentation within the comments on the draft decision. Furthermore, you have provided a copy of the robust study summaries of a repeated dose toxicity study (90-day) according to OECD TG 408 and a prenatal developmental toxicity study with rats according to OECD TG 414 performed with the source substance that are available in the IUCLID dossier for the source substance dibutylfumarate (also referred to as DBF).

You use the following arguments to support the prediction of properties of the registered substance subject to this decision from data for DBF:

- *"DOF and DBF are very similar molecules; the only difference is the length of the carbon chain on both ends of the fumarate group. This difference in length of the carbon chains is reflecting in several physical/chemical parameters, such as density, molecular weight, vapor pressure, log Kow and water solubility;*
    - *The pre-natal developmental toxicity study (OECD 414) of DBF does not show any potential of reproduction toxicity.*
    - *In the 90 day study of DOF (OECD 408) no toxicologically significant changes were noted in any of the other parameters investigated in this study (i.e. clinical appearance, functional observations, ophthalmoscopy, body weight, food consumption, clinical laboratory investigations and macroscopic examination). No adverse effects were observed in the reproductive organs examined in this study. Spermatogenic staging profiles were normal for all males examined.*
- *The metabolites of DOF and DBF are both resulting in an alcohol and fumaric acid; 2-ethylhexan-1-ol and fumaric acid do not indicate any potential of reproduction toxicity.*

[2] 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).

Therefore performing a Pre-natal developmental toxicity study (OECD 414) with DOF will not generate significantly different information."

ECHA considers that this information is your read-across hypothesis, which provides the basis whereby you predict the properties of the registered substance from the source substances.

b) ECHA's evaluation and conclusion

ECHA notes that although there is structural similarity between the registered substance DOF and the source substance DBF with respect to the fumarate moiety, there are also remaining significant structural difference (2-ethylhexan- versus butan-moiety). The data you have provided indicate that both substances have different toxicokinetic and toxicological profiles. More specifically, physicochemical parameters, *e.g.* water solubility and logKow, indicate that dibutylfumarate could be more bioavailable than the registered substance but no toxicokinetic data has been provided for any of the substances. In addition, you cite that no effects were observed for the registered substance in a sub-chronic toxicity study at the highest dose tested (1000 mg/kg bw/d) but you refer to a NOAEL of 50 mg/kg bw/d for dibutylfumarate based on effects in the kidneys. Therefore, the claim that the structural similarity in both substances results in a similar toxicity is not supported by the data. This impedes the prediction of properties. Therefore, your hypothesis does not provide a basis for predicting the properties in question of the registered substance from the source substance.

With respect to the information you referred to in your comments on the metabolites of the registered substance (2-ethylhexan-1-ol and fumaric acid), ECHA notes that you cite a pre-natal developmental toxicity study with 2-ethylhexan-1-ol, but you did not provide a robust study summary enabeling ECHA to independently evaluate this study. Furthermore, you did not provide information on pre-natal developmental toxicity study for fumaric acid, the another predicted metabolite of the registered substance. In addition, the data provided for repeated dose toxicity with the registered substance (NOAEL 1000 mg/kg bw/d) and the metabolites 2-ethylhexan-1-ol (NOAEL 250 mg/kg bw/d) and fumaric acid (NOAEL 600 mg/kg bw/d) indicate that the metabolism of the registered substance to its metabolites is not instantaneous. Hence, it can be expected that the registered substance and its third predicted metabolite, the monoester 2-ethylhexylfumarate, are systemically available and hence, their toxicity needs to be considered in the read-across approach. However, you did not provide supporting information for the registered substance (*e.g.* from a screening study) that on developmental toxicity of the registered substance to be used in your read-across approach as a 'bridging study' comparing effects for source and target substances. Therefore, your hypothesis does not provide a basis for predicting the properties of the registered substance from its metabolites.

c) Conclusion on the grouping and read-across approach

For the reasons as set out above, ECHA considers that this grouping and read-across approach does not provide a reliable basis whereby the human health effects of the registered substance may be predicted from data for reference substance(s) within the group. Hence, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation. ECHA notes that there are specific considerations for the individual endpoints which also result in a failure to meet the requirement of Annex XI, 1.5, and these are set out under the endpoint concerned.

As described above, further elements are needed to establish a reliable prediction for

toxicological or ecotoxicological properties, based on recognition of the structural aspects the chemical structures have in common and the differences between the structures of the source and registered substances. This could be achieved (if it is possible) by a well-founded hypothesis of (bio)transformation to a common compound(s), or that the registered and source substance(s) have the same type of effect(s), together with sufficient supporting information to allow a prediction of human health properties.

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

A "pre-natal developmental toxicity study" (test method EU B.31./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 sought to adapt this information requirement according to Annex IX, Section 8.7., column 2 according to which the study does not need to be conducted if "*the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentration below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled aire) and there is no or no significant human exposure*".

You provided the following justification for the adaptation: "*The lead registration dossier is for a substance manufactured or imported at > 100 t/a and a 90-day repeated dose toxicity study was performed in accordance with Section 8.6.2 of column 1, Annex IX. Registrants note that Annex I, 0.5 last paragraph applies. It was be demonstrated that the substance is of low toxicological activity and that no systemic absorption occurs via relevant routes of exposure (plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air). No adverse effects were observed in the reproductive organs examined in this study. Spermatogenic staging profiles were normal for all males examined. There is also no significant human exposure.*

Depending on the results of that 90-days toxicity study the pre-natal developmental toxicity study and the two-generation reproductive toxicity study will be either waived or conducted, based on section 8.7 of column 2, Annex IX (The studies do not need to be conducted if ... the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure."

However, your adaptation does not meet the specific rules for adaptation of Annex IX, Section 8.7., column 2, because although the substance could be of low toxicological activity based on the data you have provided, you have not provided any toxicokinetic data to prove that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air).

In addition, no or no significant human exposure is not supported based on the description of the lifecycle of the registered substance which contains process categories which might

lead to significant exposure, like for instance PROC 8a, 8b and 9. Therefore, your adaptation of the information requirement is rejected.

In your comments on the draft decision according to Article 50(1) of the REACH Regulation you have proposed a read-across approach from data obtained for a structurally-similar substance, dibutylfumarate and from the metabolites of the registered substance. However, as explained above under "*Grouping of substances and read-across approach*" your adaptation does not meet the specific rules for adaptation of Annex XI, Section 1.5.

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 EU B.31./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) R.7a, chapter 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: EU B.31./OECD TG 414) in a first species (rat or rabbit) by the oral route.

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).

As addressed under section 1 (Pre-natal developmental toxicity study in a first species) you have sought to adapt this information requirement according to Annex X, Section 8.7., column 2, according to which the study does not need to be conducted if "*the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentration below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled aire) and there is no or no significant human exposure*".

However, as explained above, your adaptation does not meet the specific rules for adaptation of Annex X, Section 8.7., column 2. Therefore, your adaptation of the information requirement is rejected.

In your comments on the draft decision according to Article 50(1) of the REACH Regulation you have proposed a read-across approach from data obtained for a structurally-similar substance, dibutyl fumarate and from the metabolites of the registered substance. However, as explained above under "*Grouping of substances and read-across approach*" your

adaptation does not meet the specific rules for adaptation of Annex XI, Section 1.5. In addition to what has been highlighted, ECHA notes that you have not provided information on prenatal developmental toxicity with a second species.

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 EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with rabbits or rats as a second species, depending on the species tested in the first pre-natal developmental toxicity study.

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) R.7a, chapter 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: EU B.31./OECD TG 414) in a second species (rabbit or rat) by the oral route.

Notes for your consideration

You are reminded that before performing a pre-natal developmental toxicity study in a second species you must consider the specific adaptation possibilities of Annex X, Section 8.7., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species with other available information enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement.

3. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 6.0, July 2017).

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

a) The information provided

You have sought to adapt this information requirement according to Annex X, Section 8.7., column 2 with the same justification as for your adaptation of the pre-natal developmental toxicity studies.

However, as explained above under "Section 1 (Pre-natal developmental toxicity study in a first species)" your adaptation does not meet the specific rules for adaptation of Annex X, Section 8.7., column 2. Therefore, your adaptation of the information requirement is rejected.

In your comments on the draft decision according to Article 50(1) of the REACH Regulation you have proposed a read-across approach from data obtained for a structurally-similar substance, dibutyl fumarate and from the metabolites of the registered substance. However, as explained above under "*Grouping of substances and read-across approach*" your adaptation does not meet the specific rules for adaptation of Annex XI, Section 1.5.

In addition, while you have referred to a two-generation reproductive toxicity study with fumaric acid, you have not provided a robust study summary for this study and you have not provided information on two-generation reproductive toxicity study or extended-one generation reproductive toxicity study with either 2-ethylhexan-1-ol *and* 2-ethylhexylfumarate or DBF.

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. Thus, an extended one-generation reproductive toxicity study according to Annex X, Section 8.7.3. is required. The following refers to the specifications of this required study.

b) The specifications for the study design

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should 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 because there is no substance-specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 6.0, July 2017). Ten weeks exposure duration is supported also by the lipophilicity of the substance (i.e. reported logKow is 7.94) to ensure that the steady state in parental animals has been reached before mating.

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a conducted range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Species and route selection

According to the test method EU B.56./ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in 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) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid with low vapour pressure, ECHA concludes that testing should be performed by the oral route.

c) Outcome

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: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, 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 the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3, if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the new information shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 6.0, July 2017). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

ECOTOXICOLOGICAL INFORMATION

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

"Growth inhibition study aquatic plants" is a standard information requirement as laid down in Annex VII, Section 9.1.2. 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.

Column 2 of Annex VII, Section 9.1.2 specifies that the study does not need to be conducted if there are mitigating factors indicating that aquatic toxicity is unlikely to occur for instance if the substance is highly insoluble in water or the substance is unlikely to cross biological membranes.

You have sought to adapt this information requirement according to Annex VII, Section 9.1.2., column 2. You provided the following justification for the adaptation: "*As cited in section 9.1.2 of column 2, Annex VII the study does not need to be conducted if there are mitigating factors indicating that aquatic toxicity is unlikely to occur. The results of the short-term toxicity test to aquatic invertebrates ("[redacted] 2005. Acute Toxicity to Daphnia") show that no adverse effects were noted up to the solubility limit of the test substance in the respective medium. Therefore aquatic short-term toxicity is considered as not likely to occur*".

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex VII, Section 9.1.2., column 2. You state in your adaptation that the results of the short-term toxicity test with *Daphnia magna* does not indicate any adverse effects up to the solubility limit of the test substance and you conclude that therefore aquatic short-term toxicity is considered not likely to occur. ECHA interprets that your above statement is meant to describe a mitigating factor that indicates "unlikely aquatic short-term toxicity".

ECHA agrees that there was no short-term toxicity in *Daphnia magna* up to the limit of water solubility. However, ECHA notes that adverse effects were observed in the long-term aquatic toxicity study with zebra fish *Danio rerio* (NOEC 0.3 mg/L) and the long-term sediment toxicity study with the midge *Chironomus riparius* (NOEC 320 mg/kg sediment dw). ECHA reminds that even though there are no indications of aquatic short-term toxicity in fish and Daphnia, the results of the requested OECD TG 201 toxicity test with algae are used to calculate both an acute (EC_{50}) and chronic ($NOEC/EC_{10}$) effect values on a different trophic level and different taxonomic group with a potentially different sensitivity to the substance. Accordingly, the "unlikely short-term toxicity for fish and Daphnia" cannot be considered a mitigating factor that is applicable to adapt the algae growth inhibition test.

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.

In your comments on the draft decision according to Article 50(1) of the REACH Regulation you accepted the evaluation made by ECHA above and agree to perform the required test.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) Algae growth inhibition test (test method EU C.3. / OECD TG 201) is the preferred test to cover the standard information requirement of Annex VII, Section 9.1.2.

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: Algae growth inhibition test, EU C.3./OECD TG 201).

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5. 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.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2 (Weight of Evidence), using an existing short-term toxicity study on *Daphnia* and an existing long-term toxicity study on fish: "*Short term Daphnia did not show any toxic effects, no indications for long term effects. Long term fish study is proposed to prove "no bioaccumulation" or "long term effects*".

However, ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI; Section 1.2. As a first line of evidence you state that "*the short-term Daphnia did not show any toxic effects*" and that there are "*no indications for long-term effects*". ECHA agrees that that there were no short-term toxic effects in *Daphnia magna* up to the limit of water solubility. However, the lack of short-term toxicity cannot be used to indicate that there are no long-term effects or that the long-term effects are unlikely because the exposure duration, the exposure concentrations and the measured effect endpoints are different in short-term and long-term tests. ECHA further notes that the registered substance has a water solubility of 1.19 mg/L at 20 °C and is therefore considered "poorly soluble". Poorly soluble substances require longer time to be taken up significantly 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 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. Therefore, long-term toxicity in *Daphnia* 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. Therefore, the first line of evidence for adapting the standard information requirement for long-term toxicity testing on aquatic invertebrates is not acceptable.

As a second line of evidence you state that "*Long term fish study is proposed to prove "no bioaccumulation" or "long term effects*". ECHA notes that a valid long-term fish toxicity study [redacted], 2013) following OECD TG 210 is available in the updated dossier. The results of the test indicate adverse effects on reproduction (number of hatched fish) and the NOEC value of 0.3 mg/l (based on mean measured concentrations) was determined to be used in Chemical Safety Assessment. Based on above, it can be concluded that the long-term fish study did not prove that there are no long term effects and no bioaccumulation. Besides, *Daphnia* and fish belong to different trophic levels and different taxonomic groups and have potentially different sensitivities to the substance. The dossier contains no evidence that *Daphnia* would have a similar or lower sensitivity than fish. Accordingly, the second line of evidence for adapting the standard information requirement for long-term toxicity testing on aquatic invertebrates is not acceptable.

This is further supported by the results of the valid OECD TG 218 long-term sediment toxicity study ([redacted], 2013) with benthic invertebrate *Chironomus riparius*, where adverse effects were seen in the midge development rate and the NOEC of 320 mg/kg sediment dw was determined to be used in Chemical Safety Assessment.

As explained above, ECHA considers that the available information in your chemical safety assessment does not rule out long-term effects to aquatic organisms such as *Daphnia* and that long-term effects on aquatic invertebrate organisms need to be further investigated. Consequently ECHA concludes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.5., column 2 and cannot be accepted.

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.

In your comments on the draft decision according to Article 50(1) of the REACH Regulation you accepted the evaluation made by ECHA above and agree to perform the required test.

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.

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 proposed 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.

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 16 November 2016.

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

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

ECHA took into account your comments and did not amend the request(s).

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

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

Appendix 3: Further information, observations and technical guidance

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

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

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

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

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