ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 5 July 2019

Addressee: [redacted]

Decision number: TPE-D-2114465664-40-01/F
Substance name: 1,4-Benzenedicarboxylic acid, mixed Bu and 2-ethylhexyl diesters
EC number: 946-149-3
CAS number: 1571954-81-8
Registration number: [redacted]
Submission number: [redacted]
Submission date: 21/12/2017
Registered tonnage band: Over 1000

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation ((EC) No 1907/2006) (the REACH Regulation), ECHA examined your testing proposal(s) and decided as follows.

Your testing proposal is accepted and you are requested to carry out:

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

Your testing proposal is modified and you are requested to carry out:

2. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: 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 systemic toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation;**
   - **Cohorts 2A and 2B (Developmental neurotoxicity)**

You have to submit the requested information in an updated registration dossier by ***12 January 2022***. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons for 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.

EUROPEAN CHEMICALS AGENCY

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 Wim De Coen, 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

The decision of ECHA is based on the examination of the testing proposals submitted by you and scientific information submitted by third parties.

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

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

Pre-natal developmental toxicity studies on two species are part of the standard information requirements for substances 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 dossier contains a pre-natal developmental toxicity study in rats as first species. However, there is no information available for a pre-natal developmental toxicity study in a second species. Consequently there is an information gap for Annex X, Section 8.7.2. and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for a pre-natal developmental toxicity study in a second species (rabbits) according to OECD TG 414.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (pre-natal developmental toxicity). ECHA notes that you provided your considerations concluding that there were no alternative methods, which could be used to adapt the information requirement for which testing is proposed. ECHA has taken these considerations into account.

In your comments to the draft decision you revised your position with regard to the alternative methods available for fulfilling the information requirement. More specifically, you believe that "*a combination of study data, publicly available data and also QSAR assessments*" can be used to fulfill the information requirement and thereby it is possible to "*avoid the unnecessary use of animals in toxicity testing.*" Furthermore, in Appendix 1 of your comments you outline on high level the metabolism and toxicity of the registered substance.

You intend to use analogue substance data with dioctylterephthalate (DOTP) (i.e. bis(2-ethylhexyl) terephthalate; EC 229-176-9; [redacted] of the registered substance composition) and terephthalic acid (EC 202-830-0). More specifically, you state that there are "*in vivo testing data available for DOTP (which is not classified for reproductive toxicity) and also for terephthalic acid* [...] *which is also not classified for developmental toxicity.*" You also assume in your comments that terephthalic acid is the common metabolite of all components of the registered substance. The comments to the draft decision could therefore be interpreted as an indication of the intent to adapt the required information on a pre-natal developmental toxicity study with a second species, possibly according to Annex XI, section 1.5. of REACH Regulation (grouping of substances and read-across approach).

However, ECHA notes you did not i) specify or provide the studies with analogue substances (DOTP and terephthalic acid) as basis of the developmental toxicity prediction, ii) provide other read-across supporting documentation explaining why and how such prediction is possible in view of the identified structural differences (e.g. structural isomers and possible stereoisomers), and iii) provide supporting evidence for such explanation. Furthermore, you

have not specified or provided any supporting data demonstrating your claims regarding metabolism and toxicity, and the registered substance being *"stable and non-toxic as it does not dissociate into mono-ester, which has toxicological effect."*

ECHA notes also that, as described in ECHA Guidance on Information Requirements and Chemical Safety Assessment (version 6.0, July 2017), section R.7.6.4.1.2. (Q)SAR, *"QSAR approaches are currently not well fitted-for-purpose for reproductive toxicity and consequently no firm recommendations can be made concerning their routine use in a testing strategy in this area."*

ECHA concludes that, in the absence of available adequate and reliable documentation in the current registration dossier, it is unable to assess the intended adaptation. ECHA notes that it is your discretion to use adequate adaptation possibilities and ECHA will review the latest dossier update only at the follow up stage once the deadline set in the decision has passed.

ECHA considers that the proposed study with the registered substance is appropriate to fulfil the information requirement of Annex X, Section 8.7.2. of the REACH Regulation.

The test in the first species was carried out with rats. According to the test method OECD 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 the rabbit as a second species.

You did not specify the route of administration for testing. 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 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a second species (rabbit), oral route (test method: OECD TG 414).

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

a) Examination of the testing proposal

Pursuant to Article 40(3)(a) and (b) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test under modified conditions.

The basic test design of an extended one-generation reproductive toxicity study (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 of the REACH Regulation. 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 in ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for an extended one-generation reproductive toxicity study according to OECD TG 415 by the oral route to be performed with the registered substance. From the information provided, ECHA understands that your reference to OECD TG 415 was accidental. ECHA understands that you actually propose to carry out an extended one-generation reproductive toxicity study, according to OECD TG 443. You have proposed the basic study design with two weeks premating period and without the inclusion of any of the extensions specified in columns 2 of 8.7.3., Annex X.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (extended one-generation reproductive toxicity study). ECHA notes that you provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

In your comments to the draft decision, you have proposed "*to address this end-point using a combination of information already available on LGFlex GL500, information from structurally related substance, publically available data and QSAR assessment*".

ECHA notes your intention to adapt the information requirement for the extended one-generation reproductive toxicity study. However, you have not provided documented data on the "*information from structurally related substance, publically available data and QSAR assessment*". Regarding "*information already available on LGFlex GL500"*, as part of your justification for the testing proposal, you have concluded that the available data in the registration dossier (including the experimental data: OECD TG 422 and OECD TG 408) are not adequate to adapt the information requirement for the extended one-generation reproductive toxicity study according to the general adaptation possibilities of Annex XI. Hence, in the absence of adequate and reliable documentation in the registration dossier on an adaptation, ECHA is unable to assess the intended adaptation. ECHA notes that it is your discretion to use adequate adaptation possibilities and that ECHA will examine any information submitted in consequence of this decision after the expiry of the deadline for provision of the information set by this decision.

ECHA considers that based on currently available information the proposed OECD TG 443 test method is appropriate to fulfil the information requirement in accordance with column 1 of Section 8.7.3., Annex IX, of the REACH Regulation.

However, ECHA considers that your proposed study design does not meet the conditions of column 2 of Section 8.7.3., Annex IX for the reasons described in the following.
Pre-mating exposure duration and dose-level setting

You proposed two weeks pre-mating exposure duration for parental animals. You have justified that there is no effect on spermatogenesis or sperm integrity, and oestrous cycle in the OECD TG 422 study.

To ensure that the study design adequately addresses the fertility endpoint, the duration of the pre-mating 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 pre-mating 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 pre-mating exposure duration is required if there is no substance specific information in the dossier supporting shorter pre-mating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.6 (version 6.0, July 2017). In this specific case ten weeks exposure duration is supported by the lipophilicity of the substance to ensure that the steady state in parental animals has been reached before mating.

Based on the available information, ECHA considers that ten weeks pre-mating exposure duration is needed to adequate investigate the sexual function and fertility for your substance.

The highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no relevant data to be used for dose level setting, it is recommended that results from a 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.

Extension of Cohort 1B

If the column 2 conditions of 8.7.3., Annex X are met, Cohort 1B must be extended, which means that the F2 generation is produced by mating the Cohort 1B animals. This extension provides information also on the sexual function and fertility of the F1 animals.

You proposed not to include an extension of Cohort 1B. You have justified your proposal with the observation that the substance would have no effect on reproductive organ and/or reproductive function seen from the studies performed according to OECD TG 408 or OECD TG 422.

However, ECHA considers that the criteria set in column 2 of Section 8.7.3. of Annex X, and which are further elaborated in ECHA Guidance on information requirements and chemical safety assessment Chapter R.7a Section R.7.6 (version 6.0, July 2017), demand the extension of Cohort 1B to include the F2 generation, because (a) the substance has uses leading to significant exposure of consumers and professionals, (b) there are indications that the internal dose for the substance will reach a steady state in the test animals only after an extended exposure, and (c) there are indications for endocrine-disrupting modes of action.

More specifically, the use of the registered substance in the joint submission is leading to significant exposure of consumers and professionals, because the registered substance is used as coatings and inks by professionals (PROCs 8a, 10, 11, and 19) and consumers (PC 9a). In addition, the substance is used in articles by consumers (AC 13a and AC 13b).

In addition, there are indications that the internal dose for the registered substance will reach a steady state in the test animals only after an extended exposure, because the partition coefficient logKow for the registered substance is between 5.5-8.4 (at 25°C and pH 7-9). As also expressed in the ECHA Guidance on information requirements and chemical safety assessment (version 6.0, July 2017) Chapter R.7a, in Appendix R.7.6–2, ECHA considers that an octanol-water partition coefficient (logKow) value (e.g. above 4.5) indicates (bio)accumulative potential.

Furthermore, there are indications for endocrine-disrupting modes of action. Specifically, hypertrophy of follicular epithelium in thyroid glands is seen in both sexes at 300 and 1000 mg/kg bw/day in the 90-day repeated dose toxicity study [redacted] with the registered substance (OECD TG 408, 2017). You consider the changes in thyroid as secondary to hepatic microsomal enzyme induction. In your comments to the draft decision, you have provided similar argumentation and concluded that the extension of Cohort 1B is "*not considered necessary*". However, you have not substantiated your claim with supportive evidence on enzyme activity measurements. In addition, effects in the thyroid gland without liver findings are observed at the mid dose level, which does not support your hypothesis. Furthermore, in your comments to the draft decision, you have questioned whether ECHA has taken into account during the evaluation the review by [redacted] (2017). ECHA reassures that this conclusion is drawn after carefully considering the information provided in the registration dossier that includes a limited robust study summary for the study, without actual quantitative results allowing an independent evaluation of the data, as well as the review by [redacted] (2017). You have not provided factual data to support your hypothesis that the changes in thyroid gland are mediated by effects on thyroid hormone metabolism, or other specific mechanisms and would be irrelevant for human.

Accordingly, the finding in thyroid (histopathological changes in thyroid gland, with or without changes in thyroid hormone levels), is considered as an indication of modes of action related to endocrine disruption and a relevant trigger.

In your comments to the draft decision, ECHA notes your claim that the test material for the 90-day study ([redacted]) is [redacted] which constitute [redacted] of the registered substance. However, ECHA considers that this study has been conducted using the registered substance, because the robust study summary for this study indicates the registered substance as the test material.

Therefore, ECHA concludes that Cohort 1B must be extended to include mating of the animals and production of the F2 generation.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity as described in column 2 of 8.7.3., Annex X. When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.

You proposed not to include Cohorts 2A and 2B because no neurotoxicity was observed in the 90-day repeated dose toxicity study (OECD TG 408, 2017) and reproductive/developmental toxicity screening study (OECD TG 422, 2017), both conducted with the registered substance.

However, ECHA notes that evidence on specific mode(s) of action with an association to (developmental) neurotoxicity is seen in the 90-day study (OECD TG 408, 2017). More specifically, hypertrophy of follicular epithelium in thyroid glands is seen in both sexes at 300 and 1000 mg/kg bw/day.

In your comments to the draft decision, you have considered that the inclusion of "*Cohorts 2A and 2B to be unnecessary and totally against the Principles of the 3R's*".

However, ECHA considers the effects in thyroid as not secondary to liver changes for the reasons explained above in section 'Extension of Cohort 1B'. Disturbed functioning of thyroid gland creates a particular concern for developmental neurotoxicity.

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

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity as described in column 2 of 8.7.3., Annex X.

You proposed not to include Cohort 3.

You have justified that the registered substance "*is not expected to be developmental immunotoxicant*". Specifically, you have stated that no effect was seen in the haematology parameters, lymphoid tissues, organ weight or histopathology examined in the 90-day study (OECD TG 408, 2017). There is also no relevant triggers from the reproductive/developmental toxicity screening study (OECD TG 422, 2017).

However, ECHA notes that thymus effects were observed in the 90-day study: thymus atrophy in females (3/10) at the mid dose level, and lymphoid depletion and thymus atrophy in males (4/10) at the mid and high dose level in the presence of histopathological changes in stomach (including hyperplasia, mucosal erosion) in the 90-day study. ECHA agrees that the effects seen in the thymus occurred in the presence of stomach irritation in the 90-day study and is likely secondary to the stress and does not indicate direct immunotoxicity of the substance. Furthermore, the haematological findings in the reproductive/developmental toxicity screening study (OECD TG 422, 2017) seem to be secondary to the kidney injury and reduction in thymus weight as secondary to stress.

Therefore, ECHA concludes that the current available information do not support the inclusion of Cohort 3 and you are not required to conduct it.
Species and route selection

You did not specify the species for testing. According to the test method OECD TG 443, the rat is the preferred species. On the basis of this default consideration, ECHA considers that testing should be performed in rats.

You proposed testing by the oral route. ECHA agrees 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.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation.

The third party provided their considerations of the study design and stated that the basic study design (Cohorts 1A and 1B without extension) "*is considered to be appropriate in the absence of any triggers or conditions necessitating the inclusion of additional cohorts or a further generation*" using similar scientific reasoning as to your proposal. However, the third party did not provide any scientific data which would fulfil this information requirement.

c) Outcome

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, you are requested to carry out the modified study with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method 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 systemic toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation;
- Cohorts 2A and 2B (Developmental neurotoxicity)

While the specifications for the study design are given above, you shall also submit with the new endpoint study record a scientific justification on each of the following aspects: 1) length of the premating exposure duration and dose level selection, 2) reasons for why or why not Cohort 1B was extended, 3) termination time for F2 generation, and 4) reasons for why or why not Cohorts 2A/2B and/or Cohort 3 were included.

Notes for your consideration

No triggers for the inclusion of Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including Cohort 3, if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the available information, together with 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*, Chapter R.7a, Section 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.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 21 December 2017.

ECHA held a third party consultation for the testing proposals from 21 May 2018 until 5 July 2018. ECHA did not receive information from third parties.

This decision does not take into account any updates after **31 October 2018**, 30 calendar days after the end of the commenting period.

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 decision does not imply that the information provided in your registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the 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 the Member States.

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.