EUROPEAN CHEMICALS AGENCY

Helsinki, 31 August 2018

Addressee: [redacted]

Decision number: TPE-D-2114440312-64-01/F
Substance name: Bis[C5-(branched)-alkyl]l benzene-1,4-dicarboxylate
EC number: 940-272-6
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 6 February 2018
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 proposals are accepted and you are requested to carry out:

1. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats using the registered substance;**
2. **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 using the registered substance;**

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

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) with extension to mate the Cohort 1B animals to produce the F2 generation.

You are additionally requested to perform:

4. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rabbit or rat), oral route using 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 an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by ***7 March 2022*** except for the information requested under point *[1]* for a sub-chronic toxicity study (90-day) which shall be submitted in an updated registration dossier by ***9 September 2019***. You may only commence the extended one-generation reproductive toxicity study as requested under point *[3]* after ***9 December 2019***, unless an indication to the contrary is communicated to you by ECHA before that date. You shall also 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.

Appeal

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

Authorised[1] by Ofelia Bercaru, Head of Unit, Evaluation E3

[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.

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)

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

A sub-chronic toxicity study (90 day) is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. 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 a sub-chronic toxicity study (90 day) in rats by the oral route according to EU B.26./OECD TG 408.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Sub-chronic toxicity (90-day): oral. 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.

You proposed testing by the oral route. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA agrees that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance is a liquid of very low vapour pressure and no uses with spray application are reported that could potentially lead to aerosols of inhalable size. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

Therefore, ECHA considers that the proposed study performed by the oral route with the registered substance is appropriate to fulfil the information requirement of Annex IX, Section 8.6.2. of the REACH Regulation.

You proposed testing in rats. According to the test method EU B.26./OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

In your comments to the draft decision and in the dossier update submitted on 6 February 2018 you explain that you intend to fulfil the information requirements addressed in this decision using a read-across approach based on information on the hydrolysis products of the registered substance (DiPT), i.e. terephtalic acid (TPA) and branched and linear pentanols.

In order to support your claim of hydrolysis of DiPT you refer to the work by Ball et al. (2012) who described a two-step metabolic pathway for terephthalate esters and concluded that the members of their terephthalate esters category are all hydrolysed to terephtalic acid (TPA) and the respective alcohol moieties. You also refer to *in vitro* data on hydrolysis

of other diesters (Batelle, 2007) to claim a limited systemic bioavailability of the parent ester DiPT.

On that basis, you indicate that you intend to conduct a metabolism study with DiPT to verify the hypothesis of rapid hydrolysis to TPA and the related alcohols. Based on the results of the metabolism study you plan to apply an analogue approach, i.e. use the available or upcoming data on (assumed) metabolites TPA and pentanols to predict the properties of the registered substance.

You expressed your intention to update the dossier within the allowed timeline with publicly available data on primary metabolites, study plan for the metabolism study and an initial read-across assessment. You further indicate that the full read-across approach justification and the complete set of data, including the source studies and the supporting data is not yet existing but will become available by the time the ongoing investigations on reaction mass of 2-methylbutan-1-ol and pentan-1-ol are finalised.

ECHA takes stock of your intention to apply a read-across approach to fulfil the information requirements addressed in this decision. According to Article 40(1) ECHA shall examine any testing proposal set out in a registration. Since the testing proposals evaluated in this decision are still included in the dossier update submitted on 06 February 2018, ECHA has the obligation to continue their evaluation according to the procedure laid down in Articles 50 and 51. In your comments to the draft decision you have not provided new scientific information leading to a modification of the evaluation of these testing proposals. Therefore ECHA has not amended the information requested in this decision.

Nevertheless, ECHA has reviewed the newly proposed read-across approach and concludes that as currently presented it does not meet the requirements of Annex XI, Section 1.5 of the REACH Regulation for the reasons detailed below.

ECHA stresses that for a read-across approach based on metabolism (RAAF Scenario 1) reliable data establishing rapid and complete hydrolysis of the parent substance is essential to support the read-across hypothesis.

Comprehensive reliable information on hydrolysis of the registered substance is particularly important since you indicated in your comments that "*the hydrolysis rate can differ mainly in the rate of metabolism, particularly concerning the second ester linkage*". This suggests that concomitant systemic exposure to both first hydrolysis products of DiPT, i.e. monoesters of terephtalic acid and the related alcohol, may occur. In the information provided in your updated dossier you have not considered the impact of systemic exposure to the monoesters, in conjunction with the related alcohol.

You expressed in your comments and in the updated dossier your intentions to "*assess DiPT as a member of the terephthalate ester category described by Ball et al (2012) (...) in order to integrate the read-across of DiPT to its primary metabolites into the described category and thus to strengthen the confidence in the overall assessment*". ECHA observes that no information on this terephthalate ester category developed by Ball et al. is currently included in your dossier. Therefore the relevance and adequacy of this category to support your revised read-across approach cannot be assessed.

ECHA understands that you consider that the properties of the substance subject to this decision can be predicted from data obtained from its hydrolysis products. In addition to the toxicokinetic considerations presented above, ECHA stresses that such predictions can only

be valid if adequate and reliable information on each hydrolysis product formed meeting the requirement of Annex XI, Section 1.5 of the REACH Regulation for an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3) is included in your technical dossier for each endpoint concerned.

ECHA also understands from the information provided in table 2 in your comments and reflected in the updated dossier that you intend to use data generated using 3-methylbutan-1-ol (EC No 903-139-3) or a reaction mass of 2-methylbutan-1-ol and pentan-1-ol as source data to predict the properties of the alcohol hydrolysis products of DiPT. ECHA notes that 3-methylbutan-1-ol is not anticipated to be formed from hydrolysis of DiPT and no explanation establishing why and how data on 3-methylbutan-1-ol is relevant for predicting properties of the alcohol hydrolysis products of DiPT is provided.

ECHA further notes that the registered substance is a UVCB substance. As part of a read-across approach on UVCB substances, particular considerations should be paid to the impact of co-exposure to the different constituents and to the variability in the concentration of these constituents in the composition of the target substance. ECHA has published considerations related to read-across on multi-constituents and UVCB substances. https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316

In your updated dossier you have provided information from a series of studies that you plan to use as part of the read-across approach:

1) Fifteen Week Oral Toxicity Studies of Terephthalic Acid – Albino Rats with Terephthalic acid (TPA). Reliability 4 (not assignable).
2) Study on the oral toxicity of 3-methylbutan-1-ol in rats Administration via the drinking water over 3 months. Reliability 1. OECD 408.
3) A Ninety-Day Study of Terephthalic Acid; Induced Urolithiasis and Reproduction Performance in Wistar and CD Rats. Reliability 4.
4) OECD 416 with Terephthalic Acid, rat. Reliability 4.
5) OECD 416 with Di-2-Ethylhexyl Terephthalate (DEHT), rat. Reliability 2.
6) Equivalent or similar to OECD 414 with Terephthalic acid (TPA), rat. Reliability 4.
7) OECD 414 with Di-2-Ethylhexyl Terephthalate (DEHT), rat. Reliability 1.
8) OECD 414 in rats with 3-methylbutan-1-ol, rat. Reliability 1.
9) OECD 414 with Di-2-Ethylhexyl Terephthalate (DEHT), mouse. Reliability 1.
10) OECD 414 with 3-methylbutan-1-ol, rabbit. Reliability 1.

ECHA observes that you have assigned a reliability index 4 (not assignable) for studies 1), 3), 4) and 6) conducted with terephthalic acid. The level of reporting of these studies in your dossier does not allow ECHA to conduct an independent assessment of the relevance and reliability of this information for hazard identification. In the absence of further details on the design and results of these studies, ECHA considers that this information cannot be used as source studies in a read-across approach intended to predict the properties of DiPT. ECHA notes that the other 6 studies reported as source studies and listed above have been conducted with 3-methylbutan-1-ol or with Di-2-Ethylhexyl Terephthalate (DEHT). These studies provide reliable information on the properties of the substances tested. ECHA understands that you consider that the properties of the substance subject to this decision can be predicted from data obtained from its hydrolysis products. However, ECHA notes that neither 3-methylbutan-1-ol or with Di-2-Ethylhexyl Terephthalate (DEHT) are not anticipated to be formed from hydrolysis for DiPT. No explanation establishing why and how data on 3-methylbutan-1-ol and DEHT is relevant for predicting properties of the alcohol

hydrolysis products of DiPT is provided. Therefore, in the absence of further information, ECHA considers that these studies cannot be used as source substances as part of the read-across approach presented in your dossier."

ECHA notes that all of the shortcomings addressed above need to be addressed, if you intend to continue with your read–across approach. If this is the case, ECHA will assess in the follow-up process according to Article 42 of the REACH Regulation whether the provisions of Annex XI, Section 1.5 are met. In this regard ECHA points out that read-across approaches are assessed using the Read-Across Assessment Framework (https://echa.europa.eu/documents/10162/13628/raaf_en.pdf/614e5d61-891d-4154-8a47-87efebd1851a).

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: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26./OECD TG 408).

Notes for your consideration

ECHA notes that a revised version of OECD TG 408 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).

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

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

A pre-natal developmental toxicity study for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. 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 a pre-natal developmental toxicity study in rats according to EU B.31./OECD TG 414 by the oral route.

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(s) for which testing is proposed. ECHA has taken these considerations into account.

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

You proposed testing in the rat as a first species. 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. On the basis of this default consideration, ECHA considers testing should be performed with rats or rabbits as a first species.

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.

In your comments to the draft decision you explain that you intend to apply a read-across approach for all requested endpoints. See ECHA response in section 1 above.

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 first species (rat or rabbit), oral route (test method: EU B.31./OECD TG 414).

Notes for your consideration

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017), Chapter R.7a, Section R.7.6.4.2.2.

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. **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) with extension to mate the Cohort 1B animals to produce the F2 generation.**

Pursuant to Article 40(3)(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 EU B.56./OECD TG 443 by the oral route with the following specifications of the study design:

"- Premating exposure duration for parental (P0) animals: Ten weeks, because there is no substance specific information supporting shorter premating exposure duration.
- Basis for dose level selection: The dose levels will be determined based on the available relevant data and based on a dose range finding study.
- Inclusion/exclusion of extension of Cohort 1B: The study design (e.g. choice of cohorts) and the necessity of this study will again evaluated if the results of the planned toxicokinetc study, 90-day study and prenatal developmental toxicity study is available.
- Termination time for F2: The study design (e.g. choice of cohorts) and the necessity of this study will again evaluated if the results of the planned toxicokinetc study, 90-day study and prenatal developmental toxicity study is available.
- Inclusion/exclusion of developmental neurotoxicity Cohorts 2A and 2B:The study design (e.g. choice of cohorts) and the necessity of this study will again evaluated if the results of the planned toxicokinetc study, 90-day study and prenatal developmental toxicity study is available.
- Inclusion/exclusion of developmental immunotoxicity Cohort 3: The study design (e.g. choice of cohorts) and the necessity of this study will again evaluated if the results of the planned toxicokinetc study, 90-day study and prenatal developmental toxicity study is available.
- Route of administration: oral
- Other considerations, e.g. on choice of species, strain, vehicle and number of animals: The study will be performed in the rat, as this is the default species according to the OECD guideline 443."

As outlined above, you also proposed to re-evaluate study design and possible inclusion of cohorts 2A and 2B and 3 when the results of the planned toxicokinetics study, 90-day study and prenatal developmental toxicity study are available.

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 for which testing is proposed. ECHA has taken these considerations into account.

ECHA considers that based on the currently available information the proposed study designs requires modification to fulfil the information requirement of Annex X, Section 8.7.3. of the REACH Regulation. More specifically, ECHA considers that the extension of Cohort 1B to include the F2 generation is required, as will be explained below in this section.

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement. Thus, an extended one-generation reproductive toxicity study according to columns 1 and 2 of 8.7.3., Annex X is

required. The following refers to the specifications of this required study.

Information from studies to be conducted before the extended one-generation reproductive toxicity study

The sub-chronic toxicity study shall be conducted before the extended one-generation reproductive toxicity study and the results from that study shall be used, among other relevant information, to decide on the study design of the extended one-generation reproductive toxicity study following ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).The sub-chronic toxicity study may provide information on effects that is relevant for triggers (e.g. weight changes and histopathological observations of organs as indication(s) of one or more modes of action related to endocrine disruption which may meet the toxicity-trigger for extension of Cohort 1B or as evidence of specific mechanism/modes of action and/or neurotoxicity and/or immunotoxicity which may meet the particular concern criteria for developmental neurotoxicity and/or developmental immunotoxicity cohorts).

Premating exposure duration and dose-level setting

You proposed ten weeks of duration for premating exposure indicating that "*there is no substance specific information supporting shorter premating exposure duration*". ECHA agrees to this with the following justification.

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 if 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* 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.

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 are 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 no extension of Cohort 1B to include F2 generation. You further proposed that "*the study design (e.g. choice of cohorts) and the necessity of this study will again evaluated if the results of the planned toxicokinetc study, 90-day study and prenatal developmental toxicity study is available*".

However, ECHA considers that there are justifications within the meaning of column 2 of 8.7.3., Annex X to now already include the extension of Cohort 1B. ECHA notes that the use of the registered substance is expected to lead to exposure of consumers and professionals. More specifically, substance is used in articles (e.g. flooring, roofing, wallpaper, sheets, coating, fabrics, textiles, paper and plastic articles, furniture coverings) which are used by workers and consumers. As you did not perform an exposure assessment, it cannot be ruled out that the exposure of consumers and professionals is not significant.

In addition, there are indications that the internal dose for the registered substance and/or any of its metabolites will reach a steady state in the test animals only after an extended exposure within the meaning of column 2 of 8.7.3., Annex X.

More specifically, you did not provide any measured toxicokinetics data on the registered substance. However, you have explained in the chemical safety report that "*The toxicokinetics of DiPT was assessed based on physico-chemical data and the available toxicological profile. The molecular weight, water solubility, octanol/water partition coefficient and QSAR predictions favours oral and inhalative absorption, whereas dermal absorption is considered to be very low. DiPT may be distributed throughout the body in a moderate way.*
Due to its lipophilicity it is expected that DiPT will tend to accumulate in adipose tissue. It is assumed that DiPT does not build reactive metabolites. In addition, it is expected that metabolites of DiPT are excreted via urine and feces".

Furthermore, as outlined above, the registered substance is lipophilic (measured log Kow is 6.6).You further explain in the chemical safety report that "*Although there is no direct correlation between the lipophilicity of a substance and its biological half-life, highly lipophilic (log P > 4) compounds tend to have longer biological half-lives. Thus, they potentially accumulate within the body in adipose tissue, especially after frequent exposure (e.g. at daily work) and the body burden can be maintained for long periods of time. After the stop of exposure, the substance will be gradually eliminated dependent on its half-life. During mobilization of fat reserves, e.g. under stress, during fasting or lactation, release of the substance into the serum or breast milk is likely, where suddenly high substance levels may be reached.<...> With the log P value of 6.6, DiPT is highly lipophilic and thus will tend to concentrate in adipose tissue during workplace exposure*".

Therefore, ECHA concludes that Cohort 1B must be extended to include mating of the animals and production of the F2 generation because the uses of the registered substance are expected to lead to exposure of professionals and consumers which cannot be ruled out as not significant and/or the internal dose for the registered substance and/or any of its metabolites will reach a steady state in the test animals only after an extended exposure.

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.

ECHA understands that you proposed not to include Cohorts 2A and 2B and provided justifications following the criteria described in column 2 of Section 8.7.3 of Annex X and detailed in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017). More specifically, you proposed that *"the study design (e.g. choice of cohorts) and the necessity of this study will again evaluated if the results of the planned toxicokinetc study, 90-day study and prenatal developmental toxicity study is available".*

ECHA agrees that the criteria to include Cohorts 2A and 2B are not met and concludes that the developmental neurotoxicity Cohorts 2A and 2B need not to be conducted.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

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. ECHA understands that you proposed not to include Cohort 3 and provided justifications following the criteria described in column 2 of Section 8.7.3 of Annex X and detailed in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017). More specifically, you proposed that *"the study design (e.g. choice of cohorts) and the necessity of this study will again evaluated if the results of the planned toxicokinetc study, 90-day study and prenatal developmental toxicity study is available".*

ECHA agrees that the criteria to include Cohort 3 are not met and concludes that the developmental immunotoxicity Cohort 3 needs not to be conducted.

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Species and route selection

You proposed testing in rats. According to the test method EU B.56./ 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.

In your comments to the draft decision you explain that you intend to apply a read-across approach for all requested endpoints. See ECHA response in section 1 above.

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 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) with extension to mate the Cohort 1B animals to produce the F2 generation.

When you update your registration dossier with the new endpoint study record for the extended one-generation reproductive toxicity study, you shall include a scientific reasoning for 1) the length of the premating exposure duration and dose level selection, 2) the need to extend Cohort 1B and termination time for F2 generation, 3) the need to include Cohorts 2A and 2B, and 4) the need to include Cohort 3, as explained in the ECHA Guidance on information requirements and chemical safety assessment (version 6.0, July 2017), Chapter R.7a, Section R.7.6.2.3.2, Stage 4.4 (iii) under the header "Study design for the extended one-generation reproductive toxicity study.

Currently, the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) are not requested. However, the sub-chronic toxicity study (90-day) requested in this decision and/or any other relevant information may trigger changes in the study design. Therefore, the sub-chronic toxicity study (90-day) is to be conducted first and the study results submitted to ECHA in a dossier update by the 12-month deadline indicated in this decision. If, on the basis of this update and/or other relevant information, a need for changes to the study design is identified, ECHA will inform you within three months after expiry of the 12-month deadline to provide the sub-chronic toxicity study (90-day), as indicated in this decision, of its intention to initiate a new decision making procedure under Articles 41, 50 and 51 of the REACH Regulation to address the design of the extended one-generation reproductive toxicity study. If you do not receive a communication from ECHA by the expiry of three months following the 12-month deadline for providing the results of the sub-chronic toxicity study (90-day), the request of the present decision for the extended one-generation reproductive toxicity study remains effective and you may commence the conduct of the study and the results will need to be submitted by the deadline given in this decision.

Notes for your consideration

When submitting the study results of the sub-chronic toxicity study (90-day) you are invited to also include in the registration update your considerations whether changes in the study design are needed (see also ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.7a, Section R.7.6 (version 6.0, July 2017)).

Furthermore, after having commenced the extended one-generation reproduction toxicity study in accordance with the ECHA decision, you may also expand this study to address a concern identified during the conduct of it and also due to other scientific reasons in order

to avoid a conduct of a new study. The justification for the changes in the study design must be documented.

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

Pursuant to Article 40(3)(c) of the REACH Regulation, ECHA may require the Registrant to carry out one or more additional tests in case of non-compliance of the testing proposal with Annexes IX, X or XI of the REACH Regulation.

Pre-natal developmental toxicity studies on two species are part of the standard information requirements for 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 outlined above under 2, ECHA has approved your testing proposal for a pre-natal developmental toxicity study in a first species according to EU B.31./OECD TG 414. ECHA notes that you registered your substance for 1000 tonnes or more per year and that your technical dossier does not contain information on a pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.). 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 in a second species (rabbit or rats), depending on the species tested in the first pre-natal developmental toxicity study.

You did not specify the route for testing as you did not submit a testing proposal for a pre-natal developmental toxicity in 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,* Chapter R.7a, Section R.7.6.2.3.2 (version 6.0, July 2017). Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

In your comments to the draft decision you explain that you intend to apply a read-across approach for all requested endpoints. See ECHA response in section 1 above.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the additional study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in a second species (rabbit or rat), oral route (test method: EU B.31./OECD TG 414).

Notes for your consideration

Before performing a pre-natal developmental toxicity study in a second species you should consider the specific adaptation possibilities of Annex X, Section 8.7.2., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species or any other new information enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement and underlying scientific justification.

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017), Chapter R.7a, Section R.7.6.4.2.2.

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).

Appendix 2: Procedural history

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

ECHA held a third party consultation for the testing proposals from 1 September 2017 until 16 October 2017. ECHA did not receive information from third parties.

This decision does not take into account any updates after **7 February 2018**, 30 calendar days after the end of the commenting period.

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).

In your comments to the draft decision you expressed your intention to apply a read-across approach for all requested endpoints (*The full read-across approach including the new metabolism study and the complete set of required information for the primary metabolites and/or category members will be available when the ongoing investigations on the reaction mass of 2-methylbutan-1-ol and pentan-1-ol will have been finalized (timeline for dossier update: 23 December 2019; decision number CCH-D-2114350942-48-01/F))*. You further state that "*We kindly ask ECHA to consider the above described strategy for future activities in this CCH process*".

ECHA understands that you request extra time (until 23 December 2019) in order to update the dossier with the final read-across approach and new studies/information. According to ECHA's standard policy such time is not provided during decision making.

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) 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.