EUROPEAN CHEMICALS AGENCY

Helsinki, 1 March 2017

Addressee: [redacted]

Decision number: TPE-D-2114355331-58-01/F
Substance name: 2,2'-ethylenedioxydiethyl bis(2-ethylhexanoate)
EC number: 202-319-2
CAS number: 94-28-0
Registration number: [redacted]
Submission number: [redacted]
Submission date: 30.09.2015
Registered tonnage band: 1000+T

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA has taken the following decision.

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

1. **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 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 of the REACH Regulation. In order 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 **9 September 2019**. You shall also update the chemical safety report, where relevant.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. 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, shall 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 proposal(s) submitted by you.

1. Extended one-generation reproductive toxicity study (Annex IX and X, Section 8.7.3.)

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* R.7a, chapter R.7.6 (version 4.1, October 2015).

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 to be performed via the oral route with the registered substance with the following justification and specification of the study design:

"*Based on the information available for 3G8, following is proposed:*
1) The EOGRTS (OECD 443), basic test design (cohorts 1A and 1B), one species (rat), most appropriate route of administration (oral), having regard to the likely route of human exposure is an Annex X (Column 1) requirement. The dosages will be derived from the existing information of subacute and subchronic toxicity studies with 3G8.
2) The duration of premating exposure (duration of dosing) should preferably be 10 weeks in males and 2 weeks in females to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility. Target organs in the subacute toxicity study in rats were the adrenal glands, kidneys, liver, pituitary gland, spleen, thymus and thyroid glands, whereas in the subchronic toxicity study only liver and kidney changes were observed in females, whereas. Bioaccumulation is not expected, and potential hydrolysis products or metabolites are considered to be rapidly eliminated or excreted.
3) The need to extend the reproduction toxicity Cohort 1B to F2 will be performed if internal triggers (described in OECD Guidance 117, 2011) for a second generation are hit during the study. Based on the available use information, exposure cannot be excluded. Therefore, trigger E1 can be considered fulfilled. With regard to the toxicity related triggers the following was noted: There was no genotoxic potential. There were no serious adverse effects of reproductive and developmental toxicity from the subacute (combined reproductive toxicity screening) and 90-day subchronic toxicity studies with 3G8. On the other hand, reduction in mean foetal body weight and increased incidence of skeletal variations (incomplete ossification of skull and delayed ossification of metatarsals and of sternal bodies) were observed at the maternally toxic dose of 1000 mg/kg/day.
One of the potential hydrolysis products (2-ethyl hexanoic acid, 2-EHA) is classified for reproductive toxicity (Repr. 2, H361d). The classification was mainly based on skeletal malformations observed in rats, but also reproductive findings were seen.

There are no qualitative nor quantitative data on the potential hydrolysis or metabolic pathway of this substance in relation to 3G8, therefore the E4 trigger is not considered to be fulfilled. Exclusion of
reproductive and developmental effects is proposed by means of an extension of Cohort 1B as described in OECD TG 443 however will be performed if internal triggers are hit (described in OECD Guidance 117, 2011). Note: As indicated in OECD TG 443, Cohort 1B animals can be maintained on treatment beyond PND 90 and bred to obtain a F2 generation if necessary. Males and females of the same dose group should be cohabited (avoiding the pairing of siblings) for up to two weeks, beginning on or after PND 90, but not exceeding PND 120. Procedures should be similar to those for the P animals. However, based on a weight of evidence, it may suffice to terminate the litters on PND 4 rather than follow them to weaning or beyond.
4) There is no need to include the developmental neurotoxicity Cohorts 2A and 2B; information from 3G8 studies (acute, subacute, subchronic) and from potential hydrolysis products/metabolites did not indicate potential (developmental) neurotoxicity.
5) There is no need to include the developmental immunotoxicity Cohort 3; information from 3G8 studies (acute, subacute, subchronic) and from potential hydrolysis products/metabolites did not indicated potential immunotoxicity. Additional immunotoxicity parameters (bone marrow cellularity, lymphocyte subtyping and T-cell Dependent Antibody Response were investigated and found to be negative in the subchronic toxicity study in rats."

ECHA considers that the proposed study design requires modification to fulfil the information requirement of Annex X, Section 8.7.3. of the REACH Regulation.

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

Premating exposure duration and dose-level setting

You proposed that "*The basic test design will be followed with 10 weeks premating duration of dosing in males and 2 weeks in females*".

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 R.7a, chapter R.7.6 (version 4.1, October 2015). 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.
In your comments on the proposal for amendment you disagree with a ten-week premating exposure duration for the following reasons: "*The lipophilicity of the substance is indeed high, purely based on the determined Log Pow value of 6.1. However, based on the findings in both the OECD422 (subacute) and OECD408 (subchronic) study, a longer duration of dosing is not expected to lead to higher toxicity, nor is it deemed required to reach a steady state.*

A longer pre-mating period for the P0 generation, in addition to the pre-mating period of 10 weeks for the F1, is not deemed necessary". However, ECHA notes that in the OECD TG 408 (subchronic) study a NOAEL of 120 mg/kg bw/day was derived based on minimal to mild liver and kidney effects observed at the highest dose of 480 mg/kg bw/day, whereas in the OECD TG 422 (subacute) study a NOAEL of 5000 ppm (314-576 mg/kg bw/day when corrected for mean test article intake) was derived (parental toxicity at the highest dose of 15000 ppm; 977-1563 mg/kg bw/day). Furthermore minimal, changes were found in the liver even at 120 mg/kg bw/day in the OECD TG 408 study. Thus, microscopic changes in liver and kidney were only observed after a longer exposure duration in the OECD TG 408 study at dose level of 480 mg/kg bw/day or marginally at even lower doses. These observations are indications that for the substance and/or any of its metabolites, to achieve an effective internal dose, an extended exposure duration is needed, and a longer duration of dosing is leading to higher toxicity in terms of lower NOAEL and LOAEL. There are no investigations of toxicokinetics available to accurately inform on the time needed to reach the steady state, or to support hypothesized hydrolysis. Thus, the lipophilicity of the substance is considered to support inclusion of longer premating exposure duration, and the reported findings in subacute and subchronic studies with difference in NOAEL by a factor up to 4.8 times further supports the longer premating exposure duration. Therefore, ECHA considers that a prolonged premating exposure duration of ten weeks is required as explained above.

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 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 to extend the reproduction toxicity Cohort 1B to F2 if internal triggers (described in OECD Guidance 117, 2011) for a second generation are hit during conduct of the study. However, ECHA considers that the extension of Cohort 1B to F2 is already triggered on the basis of the currently available information.

The use of the registered substance leads to significant exposure of consumers and professionals because the registered substance is used by professionals as an adhesive in spray applications and by consumers in sealants, paint removers, thinners and paint as a softener. Additionally, you conclude in your testing proposal justification document that "*based on the available use information, exposure cannot be excluded. Therefore, trigger E1 can be considered fulfilled.*"

Furthermore, 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. You conclude that "*Bioaccumulation potential was assessed to be low either for the parent substance and potential hydrolysis products or metabolites. Expected hydrolysis products are 2-ethyl hexanoic acid (2-EHA) and triethylene glycol (TG), for which urinary clearance and faecal excretion is known to be fast.*

Target organs seen after subchronic (90-day) dosing with 3G8 were only kidney and liver in female rats dosed at 480 mg/kg bw (see data under E4), whereas in the subacute (28-day) toxicity in rats, findings were seen in both sexes in adrenal glands, kidneys, liver, pituitary gland, spleen, thymus and thyroid glands at the highest dose approximating >1000 mg/kg bw. Longer exposure therefore did not lead to higher toxicity, confirming that bioaccumulation is unlikely".

However, the log Kow of the registered substance is 6.1 at 25°C. Thus, ECHA considers that there is a potential for accumulation of the parent substance (registered substance) but not for the hydrolysis products 2-EHA and TG which seem to show quick elimination.

In your comments on the draft decision you disagree that the E3 trigger is met stating that "*The log Kow of the substance is indeed 6.1 at 25°C. However, from this information however, it cannot be immediately concluded that the substance has a high bioaccumulative potential. It is actually quite likely that biotransformation takes place, and consequently should be taken into account. For example, this is demonstrated by QSAR modeling. As also stipulated in the CSR, BCFBAF v.3.01 QSAR modeling (EpiWeb 4.1, US-EPA model) indicates that the estimated Log BCF of the substance is reasonably low (Log BCF = 2.32; BCF = 208 L/kg wet weight), suggesting a low potential for bioaccumulation*". You also state that "*when the substance is administered orally (via gavage), the substance is expected to undergo enzymatic hydrolysis (digestion) in the aquatic environment of the gastrointestinal tract. A study by Mattson and Volpenheim (1969) indicated that enzymatic hydrolysis, by e.g. pancreatic lipase is relevant for different types of esters with varying chain lengths of C3 to C16 which is again indicative of biotransformation as the substance of concern contains two ester functionalities (C8-esters)*" but acknowledge that you "*appreciate that the evidence is not obtained on the substance itself*".

ECHA notes that the E3 trigger is fulfilled if "*there are indications that the internal dose for the substance and/or any of its metabolites will reach a steady state in the test animals only after an extended exposure*". According to ECHA's Guidance R.7a: Endpoint specific guidance Version 4.1 – October 2015, an octanol-water partition coefficient (log Kow) value (e.g. above 4.5) indicates (bio)accumulative potential (determined experimentally or estimated by QSAR models) of the substance and/or its metabolites unless the substance is fully metabolised to hydrophilic metabolites. ECHA has taken the provided data on metabolism of the registered substance into account which did not show that full metabolism to hydrophilic metabolites occurs. No data on hydrolysis (stability) and no experimental data on bioaccumulation have been provided.

In addition, there are indications for endocrine-disrupting modes of action from the available OECD TG 422 study because of adenohypophyseal multifocal hypertrophy observed in pituitary gland in males.

In your comments on the draft decision you also disagree that there are indications of endocrine disrupting modes of actions stating that "*The adenohypophyseal multifocal hypertrophy observed in the 28-day reproductive screening study was seen in male rats only, including control animals, and was not confirmed in the 90-day toxicity study*". You argue that this finding is not substantial enough to demonstrate endocrine disruption potential.

ECHA notes that the trigger "*adenohypophyseal multifocal hypertrophy*" stems from an OECD TG 422 study with lower statistical power compared to the provided OECD TG 408 study. Similar effects are not observed in the provided OCD TG 408 study with higher statistical power. However, the lack of consistency can be explained by the different dose levels used.

The OECD TG 422 study used dose levels of up to 977-1073 mg/kg bw/day, whereas the OECD TG 408 study only used dose levels up to 480 mg/kg bw/day. Therefore, ECHA considers the findings from the OECD TG 422 study with lower statistical power as a valid trigger as the differences in findings can be explained by the increased dosing.

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 is leading to significant exposure of professionals and consumers and the internal dose for the registered substance will reach a steady state in the test animals only after an extended exposure and the indications of modes of action related to endocrine disruption for the registered substance.

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

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 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* R.7a, chapter R.7.6 (version 4.1, October 2015) based on information from the registered substance and from its potential hydrolysis products/metabolites.

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.

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* R.7a, chapter R.7.6 (version 4.1, October 2015) based on information from the registered substance and from its potential hydrolysis products/metabolites.

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 4.1, October 2015) 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 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.

Deadline in the decision:

In your comments on the draft decision you request more time to provide the required study stating that "*the Registrant was informed by trustworthy Contract Research Organisations that the in-life period of the main EOGRTS study may already require 40-50 weeks. As this excludes dose range finding, analytical method validation, study plan and report generation, consortium discussions and dossier update, the 24 months is considered too short. An extension of 6 months, to bring the time allowed to 30 months, is therefore requested for the completion of this study and related dossier update. This would then also be in line with several other draft Decisions for OECD 443 studies received by other Eastman Registrants*". ECHA notes that you have not provided any documentation (e.g. letter from CRO explaining reasons for delay) showing that the extension of the 24-month deadline is justified. Therefore, the request in your comments on the draft decision for an extension of the deadline of the draft decision is rejected.

As a further comment on the draft decision submitted as part of your comments to a Member State Competent Authority (MSCA) proposal for amendment (PfA), you repeated your request for a deadline extension from 24 months to 30 months due to limited laboratory capacity. As previously ECHA did not ask you to substantiate your claim with evidence from a laboratory, at this decision making stage, ECHA requested you to substantiate your claim by 23 January 2017. You have provided sufficient documentary evidence including a letter from a number of different CRO's on the timelines to support your claim that further time is needed. Based on the documents received, ECHA considers a deadline of 30 months is a reasonable time period for providing the required information in the form of an updated registration from the date of the adoption of the decision. The decision was therefore modified accordingly.

Note for your considerations:

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 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.7.a, chapter R.7.6 (version 4.1, October 2015). 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.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposal(s) for examination pursuant to Article 40(1) on 13 June 2014.

ECHA held a third party consultation for the testing proposal(s) from 18 September 2014 until 3 November 2014. ECHA did not receive information from third parties.

This decision does not take into account any updates after **3 August 2016**, 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 on 27 May 2016 and invited you to provide comments.

ECHA received your comments on the draft decision on 4 July 2016.

The ECHA Secretariat considered your comments. This has been reflected in the Appendix 1 (Reasons) whereas the information required was not amended.

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

ECHA received proposals for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

In addition, you provided comments on the draft decision. These comments were not taken into account by the Member State Committee as they were considered to be outside of the scope of Article 51(5).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-52 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This 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 request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

3. In relation to the information required by the present decision, the sample of the substance used for the new test(s) 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 test(s) 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 test(s) must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.