EUROPEAN CHEMICALS AGENCY

Helsinki, 13 November 2017

Addressee: [redacted]

Decision number: TPE-D-2114373692-42-01/F
Substance name: 2-ethylhexyl 10-ethyl-4,4-dimethyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate
EC number: 260-829-0
CAS number: 57583-35-4
Registration number: [redacted]
Submission number: [redacted]
Submission date: 14.06.2016
Joint submission tonnage band: 100 - 1000 (submission number [redacted] with latest tonnage band)

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 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.**
2. **Short-term neurotoxicity study (28-day), oral route (Annex IX, Section 8.6.1.; test method: EU B.43./OECD TG 424) in rats, oral route using the registered substance.**

Your testing proposals are modified and you are requested to carry out:

3. **Sub-chronic neurotoxicity study (90-day), oral route (Annex IX, Section 8.6.2., Column 2; test method: EU B.43./OECD TG 424) in rats, combined with the 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, as specified in Appendix I, section 3.**

Your following testing proposal is rejected:

4. **In vivo unscheduled DNA synthesis with mammalian liver cells (Annex IX, Section 8.4.; test method: OECD TG 486).**

You are required to submit the requested information under this decision in an updated registration dossier by **20 May 2020**. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to IX 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.

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 Claudio Carlon, Head of Unit, Evaluation E2

[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 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.

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 with 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 species. On the basis of this default consideration, ECHA considers testing should be performed with the rat or the rabbit as a first species.

You did not specify the route 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) 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.

Following the proposals for amendment (PfA) submitted by one of the Members' State Competent Authority (MSCA), it was proposed to delay the pre-natal developmental toxicity study so as to allow the findings of the 90-day sub-chronic / neurotoxicity study (as requested under section 3 of this decision). If neurotoxicity is confirmed a standard pre-natal developmental toxicity study would not thoroughly address this concern and that a novel study design would be necessary. Alternatively, it was proposed to amend the deadline so as to introduce standard sequential testing. In your comments on the PfA you agree that the pre-natal developmental toxicity study should be delayed to wait for the results of the 90-day sub-chronic / neurotoxicity study. Additionally, you request ECHA to reconsider the deadline due to the anticipated demand for testing which is likely to be higher than normal, at least after end of May 2018.

In response to your comments, ECHA considers that the reasons brought forward by you are not as such to justify the delay of the pre-natal developmental study, as explained below. Firstly, if neurotoxicity is confirmed based on the 90-day sub-chronic / neurotoxicity study then a modified pre-natal developmental toxicity study may not be the appropriate study to follow and the developmental neurotoxicity study (OECD TG 426) could be needed to address this concern, subject to the (potential) separate testing proposal process (Annex IX, Section 8.7.3., column 2 of the REACH Regulation). Secondly, ECHA notes that the pre-natal developmental toxicity study and the developmental neurotoxicity study investigate different hazardous properties and are not interchangeable. Hence the pre-natal developmental toxicity study as required in the current decision is still needed as it is a standard information requirement and there is currently no other information in the dossier to fulfil this endpoint. Thirdly, ECHA notes that you have not provided any case-specific reasons to justify your request for reconsideration of the deadline. Additionally, ECHA notes that the deadline of 30 months in the draft decision has already been set to allow for sequential testing for the requested studies.

Outcome

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.7.6.2.3.2.

2. Short-term neurotoxicity study (28-day) (Annex IX, Section 8.6.1.)

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

A short-term toxicity study (28-day) is a standard information requirement as laid down in Annex IX, Section 8.6.1. of the REACH Regulation, if tests according to Section 8.6.2 of this Annex is proposed. Testing is proposed on the basis set out in column 2 of Annex IX, Section 8.6.2 (see below).

According to Annex IX, section 8.6.2., column 2 of the REACH Regulation, further studies shall be proposed by the registrant in case of "*toxicity of particular concern*" or "*indications of an effect for which the available evidence is inadequate for toxicological and/or risk characterisation*". In this case, "*specific toxicological studies*" can be performed "*to investigate the effects*", such as neurotoxicity.

You have submitted a testing proposal for a short-term neurotoxicity study (28-day) in rats by the oral route according to EU B.43./OECD TG 424.

In the technical dossier you have not provided any study record of a short-term repeated dose toxicity study (28-day) that would meet the information requirement of Annex VIII, Section 8.6.1. ECHA considers that there is a data gap. You have stated "It is proposed to conduct a 28 day neurotoxicity study as a range-finder for a 90 day neurotoxicity study. The studies will be run in sequence, not simultaneously." ECHA considers that this is an acceptable basis for performing the study, specifically in view of the concerns set out below.

In the technical dossier you claim that "*neurotoxicity is a known endpoint of concern for methyltin substances*" and that this proposed study shall "*specifically evaluate the neurotoxicity endpoint*". Moreover, in the technical dossier you provided two 90-day studies ([redacted], 1997; [redacted], 2000) with the analogue substance DMTC (EC no: 212-039-2). In both oral 90-day studies on DMTC the main target organ was the nervous system. These findings led to a harmonised classification of STOT RE 1 – H372 (causes damage to the nervous system and immune system) for DMTC. You do not consider that read-across from these analogue substances is valid, but you do consider that the information from these analogue substances gives rise to a concern.

ECHA considers that the conditions of Annex IX, section 8.6.2., column 2 are met, and that the conduct of an OECD TG 424 study is warranted because you have provided reasons to justify the proposal of this specific toxicological study to investigate neurotoxicity.

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, based on the very low vapour pressure and the high boiling point, inhalation exposure is unlikely to occur. Moreover, according to the information provided within the CSR "*inhalation exposure to the general population is near zero because any DMTE used in commercial products, e.g. PVC pipe or plastic packaging, is bound in the matrix of the plastic and unavailable for potential exposure.*" Hence, the test shall be performed by the oral route using the test method EU B.43./OECD TG 424.

You did not specify the species to be used for testing. According to the test method EU B.43./OECD TG 424 the rat is the preferred rodent species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Outcome

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: Neurotoxicity study in rodents oral route (test method: EU B.43./OECD TG 424).

Note for Registrant

ECHA notes that, if the proposed 28-day study is to serve as an effective range-finder, it is necessary to look at the same endpoints in the 28-day study, as in the 90-day study. ECHA therefore recommends you to include the same endpoints as additionally stipulated for the 90-day study (see request 3 below). However, in your comments you state that you do not plan to conduct additional post-mortem examinations that will be done in the 90-day study as you only intend to evaluate the behaviour of the test animals during the neurotoxicity study.

3. Sub-chronic neurotoxicity study (90-day) (Annex IX, Section 8.6.2.)

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

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.

According to Annex IX, section 8.6.2., column 2 of the REACH Regulation, further studies shall be proposed by the registrant in case of "*toxicity of particular concern*" or "*indications of an effect for which the available evidence is inadequate for toxicological and/or risk characterisation*". In this case, "*specific toxicological studies*" can be performed "*to investigate the effects*", such as neurotoxicity.

You have submitted a testing proposal for a sub-chronic neurotoxicity study (90-day) in rats by the oral route according to EU B.43./OECD TG 424. You claim that "*neurotoxicity is a known endpoint of concern for methyltin substances*" and that this proposed study shall "*specifically evaluate the neurotoxicity endpoint*". Moreover, in the technical dossier you provided two 90-day studies ([redacted] 1997; [redacted], 2000) with the analogue substance DMTC (EC no: 212-039-2). In both oral 90-day studies on DMTC the main target organ was the nervous system. These findings led to a harmonised classification of STOT RE 1 – H372 (causes damage to the nervous system and immune system) for DMTC. You do not consider that read-across from these analogue substances is valid, but you do consider that the information from these analogue substances gives rise to a concern.

ECHA considers that the conditions of Annex IX, section 8.6.2., column 2 of the REACH Regulation are met, and that the conduct of an OECD TG 424 study is warranted. This is because you have provided reasons to justify the proposal of this specific toxicological study to investigate neurotoxicity.

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, based on the very low vapour pressure and the high boiling point, inhalation exposure is unlikely to occur. Moreover, according to the information provided within the CSR "*inhalation exposure to the general population is near zero because any DMTE used in commercial products, e.g. PVC pipe or plastic packaging, is bound in the matrix of the plastic and unavailable for potential exposure.*" Hence, the test shall be performed by the oral route using the test method EU B.43./OECD TG 424.

You did not specify the species to be used for testing. According to the test method EU B.43./OECD TG 424 the rat is the preferred rodent species. ECHA considers this species as being appropriate and testing should be performed with the rat.

As described above, ECHA considers the neurotoxicity study (EU B.43./OECD TG 424) as a further study to investigate the neurotoxicity concern with the registered substance, as per Annex IX, Section 8.6.2., Column 2. However, ECHA notes that to fulfil the standard information requirement in the registration dossier for repeated dose toxicity, as set out in Annex IX, Section 8.6.2., you shall include additional examinations/parameters as established in test method EU B.26./OECD TG 408 on sub-chronic toxicity (90-day) study.

Hence, the neurotoxicity study in rodents (EU B.43./OECD TG 424) shall be combined with the repeated dose 90-day oral toxicity study (EU B.26./OECD TG 408) so as to include the following additional examinations and parameters to the proposed study:

1. the minimum numbers of animals to be used per group is set out in OECD TG 424, Table 1, under the column of "*neurotoxicity study conducted as: combined study with the 90-day study*";
2. organ weights and organ/body weight ratios, haematological examinations, clinical biochemistry determinations and gross necropsy should be performed as set out in the OECD TG 408; and
3. histopathological examinations should go beyond the specific neuropathology effects, since a full histopathology as set out in the OECD TG 408 is required.

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: Neurotoxicity study in rodents (test method: EU B.43./OECD TG 424) combined with the Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26./OECD TG 408), as specified above in this section.

4. In vivo unscheduled DNA synthesis with mammalian liver cells (Annex IX, Section 8.4., column 2)

Pursuant to Article 40(3)(d) of the REACH Regulation, ECHA may reject a proposed test.

"Mutagenicity" is an information requirement as laid down in Section 8.4. of Annexes VII to X of the REACH Regulation. Column 2 of Annex IX, Section 8.4. provides that "If there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII and there are no results available from an *in vivo* study already, an appropriate *in vivo* somatic cell genotoxicity study shall be proposed by the Registrant."

You have submitted a testing proposal for an "*in vivo* mammalian cell study: DNA damage and/or repair".
The technical dossier contains only one *in vitro* study: a negative gene mutation study in bacterial cells, performed according to test method OECD TG 471, with the registered substance. For the *in vitro* cytogenicity endpoint you have provided a waiver claiming that the *in vitro* study with the registered substance does not need to be conducted as "*adequate data from an in vivo cytogenicity test is available.*" Moreover, the *in vitro* gene mutation study in mammalian cells was not provided "*as two negative in vivo assays are available, in addition to a negative in vitro Ames assay.*" The *in vivo* assays provided in the dossier are with the analogue substance Dichlorodimethyl-Stannane (EC no. 212-039-2).

ECHA notes that an *in vivo* genotoxicity study with the registered substance is not required at this point since there are no positive results in the dossier that might indicate that the substance induces gene mutations and/or chromosomal aberrations. You will first need to fulfill the standard information requirements of Annex VIII, Sections 8.4.2. and 8.4.3., in order to determine the need to perform any *in vivo* studies. Hence, Annex IX, Section 8.4., column 2, does not apply due to the absence of positive results in the technical dossier.

With reference to the above-mentioned data gaps ECHA has notified you in a separate decision on a compliance check on the registered substance (2-ethylhexyl 10-ethyl-4,4-dimethyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate) of **13 November 2017, CCH-D-2114372123-58-01/F**

Outcome

Therefore, pursuant to Article 40(3)(d) of the REACH Regulation, you shall not perform the proposed "*in vivo* mammalian cell study: DNA damage and/or repair", since ECHA has rejected the proposed test.

Deadline to submit the requested information

In the draft decision communicated to you, the time line to provide the requested information was 48 months from the date of adoption of the decision. This timeline has been set to allow for sequential testing for the requests identified in that decision and other requests notified to you in a separate decision on a compliance check on the registered substance (2-ethylhexyl 10-ethyl-4,4-dimethyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate) of **13 November 2017, CCH-D-2114372123-58-01/F]**.

ECHA notes that you amended your tonnage band and downgraded it from more than 1000 tonnes per year to 100-1000 tonnes per year. Consequently, the draft request for a pre-natal developmental toxicity study in a second species (Annex X, section 8.7.2) has been removed from this decision and the time line for the remaining requests in this decision has been set to 30 months.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 14 June 2016.

ECHA held a third party consultation for the testing proposals from 1 September 2016 until 17 October 2016. ECHA did not receive information from third parties.

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when draft decision was notified to you under Article 50(1) of the REACH Regulation. Exceptionally, following your comments on the draft decision indicating a tonnage band downgrade, ECHA has taken into account the updated tonnage band (submission number: [redacted] and date: 22 March 2017). Based on the average production or import volumes for the three preceding calendar years, the tonnage band has been changed from more than 1000 tonnes per year (submission number: [redacted] from 14 June 2016) to 100-1000 tonnes per year (submission number: [redacted]).

ECHA notes that your own tonnage band is 10-100 tonnes per year but the tonnage band for several members of the joint submission is 100 to 1000 tonnes per year.

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 30 November 2016 and invited you to provide comments.

ECHA took into account your comments and your information about tonnage band downgrade and amended the draft decision. This has resulted in the removal of the following decision request: the pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species.

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

ECHA received proposal(s) for amendment and did not modify 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.

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-55 meeting 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 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 relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

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

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

   In your general comments to the draft decision pursuant to Article 50(1) of the REACH Regulation, you stated that the test substance should be a pure substance for several reasons. ECHA notes that it is your responsibility to ensure that the tested substance is suitable for use by all members of the joint registrations. ECHA further stresses that as the registrants have chosen the approach to register the constituents of their multiconstituents substances separately, the registrants must ensure that the information generated is relevant for the actual substance manufactured and that proper hazard and risk assessment are done.