EUROPEAN CHEMICALS AGENCY

Helsinki, 13 November 2017

Addressee: [redacted]

Decision number: CCH-D-2114372123-58-01/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
Registered tonnage band: 100-1000 (submission number [redacted] with latest tonnage band)

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. **Hydrolysis as a function of pH (Annex VIII, Section 9.2.2.1.; test method: EU C.7./OECD TG 111) with the registered substance;**

2. **In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method: OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2, test method: OECD TG 487) with the registered substance;**

3. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance, provided that the study requested under 2. has a negative result;**

You are required to submit the information requested under this decision in an updated registration dossier by **20 November 2018**. 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 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.

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

Appeal

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

Authorised[1] by 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

TOXICOLOGICAL INFORMATION

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

Your registration dossier contains for the endpoints *in vitro* cytogenicity study in mammalian cells (Annex VIII, 8.4.2.) and *in vitro* gene mutation study in mammalian cells (Annex VIII, 8.4.3.), adaptation arguments in form of a grouping and read-across approach. ECHA has considered first the scientific and regulatory validity of your read-across approach in general before assessing the individual endpoints (sections 2 and 3 of decision).

0. Grouping of substances and read-across approach

According to Annex XI, Section 1.5. there needs to be structural similarity among the substances within a group or category and furthermore, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). Furthermore, Annex XI, Section 1.5. lists several additional requirements, including that adequate and reliable documentation of the applied method have to be provided.

You have sought to adapt the information requirements for *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.), *in vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.) and extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.) by applying a read-across approach in accordance with Annex XI, Section 1.5.

You have considered to achieve compliance with the REACH information requirements for the registered substance [2-ethylhexyl 10-ethyl-4,4-dimethyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate (DMTE)] using data of a structurally similar substance [dimethyltin dichloride (DMTC)] (EC No. 212-039-2) (hereafter the 'source substance').

Initially you have provided read-across documentation in the CSR and in the endpoint summary in IUCLID section 7.1, under Toxicokinetics. You used the following arguments to support the prediction of properties of the registered substance from data for reference substance within the group: "*on the basis of the available data*" the registered substance hydrolyses to the source substance "*under simulated gastric conditions*".

However, you have updated the dossier (22 December 2015) (IUCLID, section 7.1.1., Basic toxicokinetics) with recent data from [redacted] (2015), on *in vitro* metabolism for the registered substance.

Following this new data you have revisited the read-across justification and concluded that the registered substance "*does not metabolize to DMTC under simulated mammalian gastric conditions [pH ~2 and 37°C] as was formerly believed*". "*DMTE is relatively stable and only partially hydrolysed to DMTEC, its mono-chloro ester by 72 hours. DMTEC is the only metabolite of DMTE formed in the simulated mammalian gastric environment. Therefore dimethyltin dichloride cannot be used as a surrogate for oral toxicity studies if compound-specific data are not available.*"
ECHA's evaluation and conclusion

ECHA notes that by updating the dossier with the above new data on *in vitro* metabolism, the interpretation of the toxicokinetics of the registered substance has changed, and the basis of the read-across justification to use the source substance to fulfill the specific endpoints is no longer valid.

You have indeed already concluded that "*the read-across from DMTC to DMTE is no longer considered to be toxicologically valid for mammalian in vivo studies on the basis of the new data, this creates possible data gaps in the dossier supporting DMTE for any data requirement which is currently fulfilled by read-across.*"

ECHA further considers that the read-across approach is not considered to be acceptable mainly because the toxicological properties of the registered substance, via the oral route, cannot be predicted from the studies carried out with the source substance. According to the study by [redacted] (2015) the registered substance does not metabolize to the source substance, but rather into another metabolite DMT(Cl)(EHTG), a metabolite, which you have not even considered in the read-across justification.

Moreover, there are other metabolites which further metabolise into potentially toxic metabolites, which have not been tested and accounted for in the read-across justification. The thioester ligand, EHTG, can also undergo further hydrolysis of the ester linkage to form thioglycolic acid (mercaptoacetic acid EC no. 200-677-4) and 2-ethylhexan-1-ol (2-EH EC no. 203-234-3). Both of these substances are classified as toxic substances. In addition, 2-EH can be further metabolised to 2-ethylhexanoic acid (EC no. 205-743-6) which is classified as Repr. 2, H316d (Suspected of damaging the unborn child).

On the basis of the reasons set above, the requirement of Annex XI, Section 1.5. of the REACH Regulation, that human health effects may be predicted from data for reference substance within the group, has not been met.

Furthermore, ECHA notes that you have provided a testing strategy justification document (under IUCLID section 13) to address the data gaps in the dossier. The proposed studies are being addressed in a separate testing proposal decision on the registered substance (2-ethylhexyl 10-ethyl-4,4-dimethyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate) of **13 November 2017, TPE-D-2114373692-42-01/F**.

1. Hydrolysis as a function of pH (Annex VIII, Section 9.2.2.1.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation.

"Hydrolysis as a function of pH" is a standard information requirement as laid down in Annex VIII, Section 9.2.2.1 of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex VIII, section 9.2.2.1, column 2. You provided the following justification for the adaptation: *"In accordance with column 2 of REACH annex VIII, the hydrolysis testing (section 9.2.2.1) does not need to be conducted if the test substance is highly insoluble in water and is considered readily biodegradable."*

ECHA notes, however, that for the endpoint "Biodegradation in water: screening test" you have provided a key study OECD 301F, kl 1, GLP, ([redacted]) where you state that "*the test item failed to satisfy the 10 Day window validation criterion, whereby 60% degradation must be attained within 10 days of the degradation rate exceeding 10%, and therefore cannot be considered to be readily biodegradable under the strict terms and conditions of OECD Guideline No 301F".* Similarly, the supporting study you provided (OECD 301F, kl.1 ([redacted])) supports this finding: *"The test substance is considered primarily biodegradable but not readily biodegradable according to OECD criteria."*

Based on the information in the technical dossier the substance cannot be considered readily biodegradable or highly insoluble (water solubility value = 4.9 mg/l). Therefore, your adaptation cannot be accepted.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Hydrolysis as a function of pH (test method: EU C.7/OECD TG 111).

2. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)

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

An "*In vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study" is a standard information requirement as laid down in Annex VIII, Section 8.4.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not provided any study record of an *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study in the dossier that would meet the information requirement of Annex VIII, Section 8.4.2.

You have sought to adapt this information requirement according to Annex VIII, Column 2 of the REACH Regulation, where the study does not need to be conducted "*if adequate data from an in vivo cytogenicity test are available*". Indeed, in the technical dossier you provided two *in vivo* study records on mammalian erythrocyte micronucleus (test guideline: OECD TG 474; [redacted], 1991) and unscheduled DNA synthesis (no test guideline; [redacted], 1993), with the proposed analogous substance dimethyltin chloride (DMTC) (EC no. 212-039-2). However, as explained in Appendix 1, Section 0 of the decision, the read-across justification of the analogous substance to the registered substance cannot be accepted, hence you have not provided such "*adequate data*" to fulfill the adaptation requirements, according to Annex VIII, column 2. Therefore, your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that the *in vitro* mammalian chromosome aberration test (test method OECD TG 473) and the *in vitro* mammalian cell micronucleus test (OECD TG 487) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.2. of the REACH Regulation.

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian chromosome aberration test (test method: OECD TG 473) or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487).

3. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

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

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained.

ECHA notes that the registration dossier does not contain an appropriate study record for this information requirement.

You have sought to adapt this information requirement according to Annex VIII, Section 8.4.3., column 2. You provided the following justification for the adaptation: "*In accordance with column 2 of REACH annex VIII, the in vitro gene mutation study in mammalian cells does not need to be conducted as (i) two negative in vivo assays are available (ii) in addition to a negative in vitro Ames assay.*"

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex VIII, Section 8.4.3., column 2, because of the following observations:

(i) The *in vivo* study records provided are with the proposed analogous substance, and as explained in Appendix 1, Section 0 of the decision, the read-across justification cannot be accepted.
(ii) Moreover, the *in vitro* gene mutation study in mammalian cells needs to be carried out if there are negative results in both the *in vitro* gene mutation study in bacteria (Ames study) and in the *in vitro* cytogenicity study in mammalian cells (or *in vitro* micronucleus study). The Ames study ([redacted], 1996) provided in the dossier has a negative result, hence if the study requested under 2. has also a negative result, the *in vitro* gene mutation study in mammalian cells shall be conducted.

Therefore, your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that the *in vitro* mammalian cell gene mutation tests using the *Hprt* and *xprt* genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490) provided that the study requested under 2. has negative results.

Deadline to submit the requested information in this decision

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. 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 an extended one-generation reproductive toxicity study (Annex X, section 8.7.3) has been removed from this decision since the criteria for triggering it, as set out in Annex IX, section 8.7.3., do not appear to be met on the basis of the available information available in the dossier. The time line for the remaining requests in this decision has been set to 12 months.

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Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when 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 however 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 1 000 tonnes per year.

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

The compliance check was initiated on 5 October 2016.

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. This has resulted in the removal of the following decision request: extended one-generation reproductive toxicity study.

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 in its MSC-55 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

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Appendix 3: Further information, observations and technical guidance

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

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

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

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

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