EUROPEAN CHEMICALS AGENCY

Helsinki, 24 April 2019

Addressee: [redacted]

Decision number: CCH-D-2114461461-54-01/F
Substance IUPAC name: ETHYL (Z,Z)-9,9-DIOCTYL-4,7,11-TRIOXO-3,8,10-TRIOXA-9-STANNATETRADECA-5,12-DIEN-14-OATE
(EC number: not applicable[1], previously 268-500-3)
(CAS number: not available)
Registration number: [redacted]
Submission number: [redacted]
Submission date: 08/06/2017
Registered tonnage band: 100-1000

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. **Name or other identifier of the substance (Annex VI, Section 2.1.);**
   - **EC and CAS entry;**
2. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**
3. **Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3; test method: OECD TG 443) in rats, oral route with the registered substance specified as follow:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce systemic toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation; and**
   - **Cohort 3 (Developmental immunotoxicity);**
4. **Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: Daphnia magna reproduction test, EU C.20./OECD TG**

[1] The technical dossier contains the following disclaimer in section 1.1: "*The EC/List entry 268-500-3 currently assigned does not specifically correspond to the registered substance since it does not consider a specific geometry of the double bonds. Based on analytical data and the manufacturing route it is most likely the Z,Z isomer. This identifier cannot be modified or deleted at this stage in the present registration update for technical reasons*". In addition, the registrant has provided the IUPAC name and deleted the CAS number in section 1.1. Therefore, this decision refers to the substance as identified by its IUPAC name, and not by EC inventory number.

211) with the registered substance

5. **Apply classification and labelling on the registered substance for chronic aquatic toxicity or provide a justification for not classifying.**

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 adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **2 November 2021**. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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[2] by **Wim De Coen**, Head of Unit, Hazard Assessment C2

[2] 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

SUBSTANCE IDENTITY INFORMATION

In accordance with Article 10(a)(ii) of the REACH Regulation, the technical dossier must contain information on the identity of the substance as specified in Annex VI, Section 2 to the REACH Regulation. In accordance with Annex VI, Section 2 the information provided has to be sufficient to enable the identification of the registered substance.

1. Name or other identifier of the substance (Annex VI, Section 2.1.)

Annex VI, section 2 lists information requirements that shall be sufficient to identify the registered substance, including the name or other identifier of the registered substance (Annex VI, 2.1.). More in detail, the information requirements listed in Annex VI, section 2.1. include: a name in the IUPAC nomenclature (section 2.1.1.), EINECS or ELINC'S number (if available and appropriate) (section 2.1.3), CAS name and CAS number (if available) (section 2.1.4). In addition the "Guidance for identification and naming of substances under REACH and CLP" (referred thereafter as the SID Guidance, available on the ECHA website) explains that a mono-constituent substance is:

- a substance, defined by its quantitative composition, in which one main constituent is present to at least 80%;
- identified by the chemical name and other identifiers (including the molecular and structural formula) of the main constituent.

On the contrary, a multi-constituent substance is a substance, defined by its quantitative composition, in which more than one main constituent is present in a concentration ≥ 10% (w/w) and <80% (w/w).

You have identified the registered substance as a mono-constituent substance with EINECS 268-500-3. This entry corresponds to the generic "ethyl 9,9-dioctyl-4,7,11-trioxo-3,8,10-trioxa-9-stannatetradeca-5,12-dien-14-oate", which refers to a multi-constituent substance consisting of all possible isomers of ethyl 9,9-dioctyl-4,7,11-trioxo-3,8,10-trioxa-9-stannatetradeca-5,12-dien-14-oate (i.e. Z,Z, E,Z and E,E isomers). You have reported CAS entry 68109-88-6 (2-butenedioic acid, 1,1'-(dioctylstannylene) 4,4'-diethyl ester) in the field "other identifiers" in IUCLID section 1.1., specifying that this identifier is used for the identification of the registered substance in other regulatory schemes.
In the manufacturing process description in IUCLID section 1.2 you stated that starting material [redacted] is used. This CAS entry [redacted] corresponds to the specific stereoisomer [redacted], and in the manfacturing process there are no steps that would lead to an isomerization of this starting material.

In addition, in IUCLID section 1.4, the analytical data (GC and NMR) confirm the mono-constituent identity of the substance. In particular, the GC chromatogram shows one sharp peak with retention time of [redacted] minutes and an area of [redacted] while the proton NMR spectrum also shows the presence of one major specific stereoisomer. This is in line with the indications reported in the SID Guidance for the identification of a mono-constituent substance (one main constituent is present to at least 80%).

Therefore, there is an inconsistency between the identifier EC 268-500-3 (relative to a multi-constituent substance) on one side and the manufacturing process description and the analytical data (relative to a mono-constituent substance) on the other side.

Based on the information given in the dossier, it seems that the registered substance should be regarded as the mono-constituent substance referring to the specific isomer where both double bonds have a Z configuration. This is also supported by your statement in the 'Remarks' field in IUCLID section 1.1 "*The EC/List entry 268-500-3 currently assigned does not specifically correspond to the registered substance since it does not consider a specific geometry of the double bonds. Based on analytical data and the manufacturing route it is most likely the Z,Z isomer. This identifier cannot be modified or deleted at this stage in the present registration update for technical reasons.*" The registered substance should be identified by the chemical name "ethyl (5*Z*,12*Z*)-9,9-dioctyl-4,7,11-trioxo-3,8,10-trioxa-9-stannatetradeca-5,12-dien-14-oate" and CAS number 52671-35-9.

Therefore, you are requested to resolve the inconsistency described above by providing the identifiers (chemical name and CAS number) that would correctly identify your substance.

As you also stated in the "Remarks" field, the EC entry 268-500-3 cannot be removed or modified at this stage, because your registration is linked to this number in REACH-IT. The statement in the "remarks" field should be kept. Instead, you should provide the correct chemical name in the "IUPAC name" field and the correct CAS entry (52671-35-9) in the "CAS information" field in IUCLID section 1.1.

In your comments according to article 50(1) of the REACH Regulation, you acknowledge that EC 268-500-3 number is not appropriate to identify the registered substance. However, you suggest including CAS number 68109-88-6 as a new identifier for the substance. Please note that CAS number 68109-88-6 is already associated with EC entry 268-500-3 with EC name "ethyl 9,9-dioctyl-4,7,11-trioxo-3,8,10-trioxa-9-stannatetradeca-5,12-dien-14-oate". Therefore, ECHA cannot associate CAS number 68109-88-6 with the new technical identifier.

You shall ensure that the chemical name, the identifiers and the manufacturing process description to be reported according to Annex VI, Section 2.1 of the REACH Regulation are consistent with each other and with the composition required to be provided according to Annex VI, Section 2.3 of the REACH Regulation.

Should the information submitted by you as a result of the present decision enable ECHA to identify the substance unambiguously, the process of adapting the identifier will be considered relevant. In that case, ECHA notes that you have already initiated the identifier adaptation process but it was not completed.

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.

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

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. 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 a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2.

You have sought to adapt this information requirement according to Annex XI, Section 3, of the REACH Regulation. You provided the following justification for the adaptation:

"In accordance with Section 3 (Substance-Tailored Exposure-Driven Testing) of Annex XI (General Rules for Adaptation of the Standard Testing Regime Set Out In Annexes VII to X) of Regulation (EC) No. 1907/2006 (REACH), which states that testing in accordance with Annex IX may be omitted, based on the exposure scenarios developed in the Chemical Safety Report, it is considered justified to omit the developmental toxicity study (required under point 8.7.2 of Annex IX)."

The results of the exposure assessment conducted as a part of the Chemical Safety Report are considered to adequately demonstrate the absence of or no significant exposure to the substance throughout the lifecycle of the substance including its manufacture and all identified uses. As such further testing for developmental effects is considered to be inappropriate.

However, ECHA notes that the information provided in the dossier does not meet the specific rules for adaptation of Annex XI, section 3. According to Article 13(1) and Section 3 of Annex XI of the REACH Regulation, testing in accordance with Annex IX may be omitted based on a thorough and rigorous exposure assessment, provided that any one of the three criteria of Section 3 of Annex XI is met and adequate justification and documentation is provided. However, none of the criteria of that adaptation are currently fulfilled.

The first criterion,3.2(a), requires "*absence of or no significant exposure in all scenarios of the manufacture and all identified uses*". Moreover, relevant PNECs or DNELs are to be derived and exposure results are to be well below the derived PNECs or DNELs. According to footnote (1) for 3.2.(a) (ii), "*For the purpose of subparagraph 3.2(a)(ii), without prejudice to column 2 of Section 8.7 of Annexes IX and X, a DNEL derived from a screening test for reproductive/developmental toxicity shall not be considered appropriate to omit a prenatal developmental toxicity study or a two-generation reproductive toxicity study*". However, the DNEL in the dossier is based on a screening study, in this case of an analogue substance, so criterion 3.2(a) cannot be fulfilled.

Further, ECHA considers that adequate and reliable documentation demonstrating the "*absence of or no significant exposure in all scenarios of the manufacture and all identified uses*" has not been provided. In several exposure scenarios for the combined routes, systemic long-term the RCRs values are close to [redacted] and the highest RCR value is up to [redacted] (PROC 24 in exposure scenario 3). In addition, the used PROCs (e.g. PROC 6, 14 and 24) indicate potential for exposure.

The second criterion, 3.2(b), requires a demonstration that "*throughout the life cycle strictly controlled conditions as set out in Article 18(4)(a) to (f)*" apply. As mentioned above, in several exposure scenarios for the combined routes, systemic long-term, the RCRs were not demonstrating strictly controlled conditions as per Annex XI, section 3.2 (b). Strictly controlled conditions are not demonstrated and therefore criterion 3.2(b) for exposure-based adaptation is not satisfied. In particular, condition (a) as set out in Article 18(4) of REACH does not appear to be fulfilled because it has not been demonstrated that the substance is rigorously contained by technical means during its whole lifecycle.

The third criterion, 3.2(c), sets out conditions which have to be fulfilled for a substance incorporated in an article, particularly that the substance is not released during its life cycle, that the likelihood of exposure of workers and general public under normal and foreseeable circumstances is negligible and that the substance is handled under the conditions set out in Article 18(4)(a) to (f) of REACH during all manufacturing and production stages including waste management. This criteria applies to your dossier, since the substance is incorporated in a plastic article (AC 13) as a stabiliser.

In the exposure scenario of service life (consumers), you state that "*the substance is only used in an industrial working environment. Exposure to humans/environment is negligible due to the inclusion of the substance in a polymer matrix. The migration out of the polymer is minimal and complies with the EU food contact migration limit in 10/2011/EU*". However, you have not demonstrated and documented the minimal release from the polymer. You also state in the risk characterisation of exposure scenario 4 that [redacted] *in closed, semi-closed or open systems*", the later suggesting exposure that does not fulfil the third criterion. Furthermore, strictly controlled conditions as set out in Article 18(4)(a) to (f) are not demonstrated, as discussed above.

Therefore, your adaptation of the information requirement is rejected.

In your comments according to article 50(1) of the REACH Regulation, you state your intention to adapt this information requirement using a PNDT study (OECD TG 414) with the analogous substance dioctyltin dioxide (DOTO). Although you do not justify the use of read-across for this endpoint in your comments, you argue elsewhere in your comments that ECHA has justified the triggering of the EOGRTS study by using the data obtained on DOTO, and so read-across to DOTO will be valid for other endpoints. ECHA points out that this triggering does not indicate that studies with the source substance DOTO constitute a reliable basis to predict properties of the registered substance from the analogous substance for this endpoint. ECHA reminds you that any adaptation according to REACH Annex XI Section 1.5, grouping and read-across, must fulfil the general rules of adaptation set out therein. ECHA observes in the case of the registered substance that there is currently no conclusive justification and documentation in your dossier that would meet these requirements.

More specifically, the provided experimental evidence does not address whether a) the registered substance undergoes sufficiently rapid and complete hydrolysis to DOTO and that its subsequent metabolism would be similar to that of DOTO, or whether b) other analogous substances would be more appropriate (e.g. dioctyltin laureate, dioctyltin chloride, etc.) to predict the properties of the registered substance. The *most adequate* choice of a source substance shall be justified and supported with experimental data. In the case of DOTO as an analogous substance, relevant differences in hydrolysis and especially solvation behaviour of the registered substance *in vivo* (as compared with DOTO) might lead to a failure to predict properties.

Additionally, c) there is currently no toxicological study available with the registered substance, such as a (combined) screening for reproductive/developmental toxicity study (OECD TG 421/422), which would allow comparison of toxicological profiles and endpoint-specific properties between the registered and (an) analogous substance(s) in support of a read-across hypothesis. Such study (or studies) would provide important extra information, in addition to the additional information on hydrolysis which is required, as discussed under

a). As a further consideration, d) ECHA reminds you that any prediction of properties shall result in appropriate risk management measures including classification.

As explained above, the information available 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.

According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first 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* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 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: Pre-natal developmental toxicity study (test method: OECD 414) in rats or rabbits by the oral route.

3. Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.)

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 IX of the REACH Regulation if the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD TGs 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. If the conditions described in column 2 of Annex IX 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).

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

a) The information requirement

You have not provided a 90-day study on the registered substance. You provided a screening study in rats [redacted] (2004) performed according to OECD TG 422 with dioctyltin oxide (DOTO, CAS no 870-08-6) which is the proposed hydrolysis product. ECHA considers you have used the study on DOTO as an adaptation according to Annex XI, 1.5 (Grouping and read-across), whereby you provide information on a read-across substance on the basis that it predicts the properties of the registered substance. In view of the results of the study on DOTO and your self-classification as STOT-RE1, ECHA considers that the read-across is 'worst-case' for the 90-day endpoint, and provides acceptable information to protect human health. ECHA considers that adverse effects on reproductive organs or tissues and other concerns in relation with reproductive toxicity are observed in

this study. More specifically, reproductive effects such as increased duration of gestation, increased implantation loss, an increased number of still born pups and pup mortality at postnatal day 4, decreased pup weight and an increased number of runts at postnatal day 1, and a statistically significant increase in the incidence of cysts in the ovaries of 8 high-dose females were seen, albeit in the high-dose only, in the presence of maternal toxicity (severe effects in thymus).

Based on the available information in your dossier, ECHA considers that there is a serious concern for reproductive toxicity and is justified further to investigate the effects in reproductive toxicity.

Pursuant to Annex IX, Section 8.7.3., an extended one-generation reproductive toxicity study is thus an information requirement for registration of the registered substance.

ECHA further notes that this OECD TG 422 study does not provide the information required by Annex IX, Section 8.7.3., because it does not cover key parameters, exposure duration, life stages and statistical power of an extended one-generation reproductive toxicity study. The main missing key aspects/elements are: at least 20 pregnant females per group, an extensive post-natal evaluation of the F1 generation, and investigation of (developmental) immunotoxicity.

You have sought to adapt this information requirement according to Section 3 of Annex XI of the REACH Regulation using the same justification as for the adaptation proposed for the prenatal developmental toxicity study (Section 2). However, ECHA notes similarly to Section 2, for the prenatal developmental toxicity, that none of the criteria of that adaptation (3.2(a); 3.2(b); or 3.2(c)) are currently fulfilled.

Therefore, ECHA considers that this adaptation of the information requirement does not meet the requirements set forth under Section 3 of Annex XI.

In your comments according to article 50(1) of the REACH Regulation, you state your intention to adapt this information requirement using an EOGRTS (OECD TG 443) performed with the analogous substance DOTO. ECHA observes that, in the case of the registered substance, there is currently no conclusive justification and documentation that would meet the general adaptation rules of Annex XI Section 1.5 REACH. ECHA notes that the deficiencies of the read-across to DOTO are already explained in Appendix 1, Section 2 of this decision, when addressing your proposed read-across for the PNDT endpoint in your comments to the draft decision. The same considerations about the read-across also apply, mutatis mutandis, for this specific endpoint. Notably, you argue in your comments that ECHA has justified the triggering of the EOGRTS study by using the data obtained on DOTO, and so read-across to DOTO will be valid for this and other endpoints. ECHA points out that this triggering does not indicate that studies with the source substance DOTO constitute a reliable basis to predict properties of the registered substance from the analogous substance for this endpoint.

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. Thus, an extended one-generation reproductive toxicity study according to columns 1 and 2 of 8.7.3., Annex IX is required. The following refers to the specifications of this required study.

b) The specifications for the required study

Premating exposure duration and dose-level setting

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 *on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017), 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 because 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 6.0, July 2017). The exposure duration is supported also by the lipophilicity of the registered substance (under the endpoint study record in IUCLID section 4.7 in the technical dossier, the reported LogKow value is >6.5 for the registered substance) to ensure that the steady state in parental animals has been reached before mating.

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

If there is no existing 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.

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 IX.

ECHA notes that existing information provided in the dossier on OECD TG 422 study ([redacted], 2004) with dioctyltin oxide (DOTO, CAS no 870-08-6), the proposed hydrolysis product of the registered substance, shows evidence of severe thymus toxicity (thymus atrophy) associated to immunotoxicity.

ECHA concludes that the developmental immunotoxicity Cohort 3 needs to be conducted because there is a particular concern on (developmental) immunotoxicity based on the results from the above-identified *in vivo* study by [redacted] (2004).

Species and route selection

According to the test method OECD TG 443, the rat is the preferred species. On the basis of this default consideration, ECHA considers that testing should be performed in rats.

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 solid, ECHA concludes that testing should be performed by the oral route.

Outcome

Based on the available information, 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: Extended one-generation reproductive toxicity study (test method OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce systemic toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation; and
- Cohort 3 (Developmental immunotoxicity).

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

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. No triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B if relevant information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the available information, together with the new information shows triggers which are described in column 2 of Section 8.7.3., Annex IX and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 6.0, July 2017). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented.

ECOTOXICOLOGICAL INFORMATION

4. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. 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 IX, Section

9.1.5., column 2. You provided the following justification for the adaptation: "*In accordance with point 9.1.5 Column 2 (Specific Rules for Adaptation from Column 1) of Annex IX of Regulation (EC) No. 1907/2006 (REACH), long-term testing on aquatic invertebrates does not need to be conducted as the chemical safety assessment concludes that the substance is of no immediate concern to the environment. The available data are adequate for classification and labelling purposes and PBT assessment, so no further testing is required*".

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.5., column 2 due to the following.

In section 4.1.1.1. "Hydrolysis of your technical dossier" you have indicated that "*Although the test material was determined to have a water solubility value of less than or equal to 1.19 x 10^-3 g/L, it has been considered that this value was a significant over-estimation, especially when contrasting the result with the calculated value of 4.7 x 10^-8 g/L, which suggests that the test material has a very low water solubility*". ECHA agrees that the registered substance can be considered as poorly water soluble. For such substances long-term aquatic testing is required, since poorly soluble substances require longer time to be taken up by the test organisms and steady state conditions are likely not reached within the duration of short-term toxicity tests. For this reason, short-term tests may not give a true measure of toxicity and long-term effects to aquatic organisms cannot be excluded. Therefore, information on long-term aquatic toxicity is needed for risk assessment and for the classification and labelling and the chemical safety assessment (CSA) cannot be used to waive the need for long-term aquatic studies.

Lastly, Annex VII 9.1.1. of the REACH Regulation explicitly recommends that long-term aquatic toxicity tests be considered if the substance is poorly water soluble. Therefore, in this case long-term data are required to accurately assess the effects of the low water solubility registered substance on aquatic organisms.

Therefore, your adaptation of the information requirement 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.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) *Daphnia magna* reproduction test (test method EU C.20. / OECD TG 211) is the preferred test to cover the standard information requirement of Annex IX, Section 9.1.5.

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: Daphnia magna reproduction test (test method: EU C.20./OECD TG 211).

Notes for your consideration

Once results of the test on long-term toxicity to aquatic invertebrates are available, you shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation. You shall also consider the results for classification and labelling, also in relation to request 5 below.

ECHA notes that in your dossier only acute aquatic data on a proposed read-across substance dioctyltin oxide (EC No 212-791-1) is available. As the registered substance is considered poorly soluble in water and long-term testing is required, short-term data alone cannot be used to conclude on risks to the aquatic environment as fully discussed in the request above. Consequently ECHA has not addressed the read-across proposed for the acute aquatic endpoints in this decision.

ECHA nevertheless notes that a read-across approach needs to fulfil the requirements set in Annex XI, Section 1.5. of the REACH Regulation and should include a full read-across justification supported with solid scientific evidence. For further advice please refer to ECHA *Guidance on information requirements and chemical safety assessment* Chapters R.6 (version 1, May 2008) and R.7.b. (version 4.0, July 2017) and ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across). Please also refer to Chapter R.7.b Table R.7.8—2 Critical parameters for aquatic toxicity testing for information on providing data on a degradation product for a parent substance.

ECHA notes also that for the derivation of the $PNEC_{aquatic,}$ data on three trophic levels, on aquatic invertebrates, fish and aquatic plants, is normally required (ECHA Guidance on information requirements and chemical safety assessment, Chapter R7b, Section R.7.8.5.3, (version, 4.0, June 2017). As discussed above, the short-term data are not adequate in this case, and long-term data on all three trophic levels would be needed for the accurate derivation of $PNEC_{aquatic}$ and to perform the chemical safety assessment. Therefore ECHA invites you to consider submitting a testing proposal for long-term toxicity testing on fish (Annex IX section 9.1.6) and to consider conducting a study to fulfil the information requirement for a growth inhibition study on aquatic plants (Annex VII section 9.1.2).

Finally, ECHA notes that due to the low solubility of the substance in water you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6/REV1 (6 July 2018) and ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

5. Hazard classification and resulting hazard label for chronic aquatic toxicity (Annex VI, 4.1. and 4.2.)

Pursuant to Article 10(a)(iv) of the REACH Regulation the technical dossier shall contain information on classification and labelling of the substance as specified in Annex VI, Section 4 of the REACH Regulation in conjunction with Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures (CLP Regulation). Annex VI, section 4.1. clarifies that the hazard classification of the substance shall result from the application of Title I and II of the CLP Regulation. In addition, for each entry, the scientifically justified reasons why no classification is given for a hazard class or differentiation of a hazard class should be provided. According to Article 5(1) of Title I and recitals 20 and 21 of the CLP Regulation, a substance shall be classified on the basis of available information.

Furthermore, the technical dossier must include the resulting hazard label for the substance in line with Title III of the CLP Regulation (Annex VI, section 4.2 of the REACH Regulation).

ECHA notes that your dossier does not contain any hazard classification for the registered substance for chronic aquatic toxicity. Based on available results on read-across substances, you have concluded that no short-term effects are to be expected up to the water solubility of the registered substance. You have considered that your substance does not meet the criteria for classification as dangerous to the environment for the following reasons: no information is available for long-term aquatic toxicity; the substance is not rapidly biodegradable; and based on a bioaccumulation study on a read-across substance, you have concluded that your substance is not bioaccumulative. However this does not seem to be supported by the available information in the technical dossier.

Pursuant to Title I and II of Regulation (EC) No 1272/2008 (CLP Regulation) and the criteria set out in Part 4 of Annex I of the CLP Regulation, as amended by Commission Regulation (EU) No 286/2011 of 10 March 2011 (Tables 4.1.0. (a) and/or (b) and 4.1.4), poorly soluble substances for which no acute toxicity is recorded at levels up to the water solubility and which are not rapidly degradable and have an experimentally determined BCF ≥500 (or if absent, a log Kow ≥4) should be classified and labelled for chronic aquatic toxicity as 'H413: May cause long lasting harmful effects to aquatic life' (Category Chronic 4).

ECHA notes that the substance is poorly soluble and is not rapidly biodegradable. Under the endpoint study record in IUCLID section 4.7 in the technical dossier, the reported LogKow value is >6.5 for the registered substance. There is no experimentally determined BCF reported for the registered substance but for a read-across substance, i.e. for dioctyltin bis(2-ethylhexyl thioglycolate) (DOT(EHTG)$_2$, CAS 15571-58-1), from the study of [redacted] (2010)[3]. Based on this data you have concluded that the BCF of the registered substance is below 100. However, there are significant issues with this latter conclusion as explained below.

The study of [redacted] (2010) was performed with two nominal test concentrations: 0.25 µg/L and 2.5 µg/L. The corresponding measured test concentrations were respectively 0.19±0.05 µg/L and 2.6±0.4 µg/L. However, no substance-specific method was available to analyse the test substance (i.e. DOT(EHTG)$_2$) with sufficient sensitivity. An indirect method designed to detect both monooctyltin compounds (MOT) and dioctyltin compounds (DOT) was used instead but this method cannot distinguish between the test substance itself or any degradation products or impurities. Therefore, ECHA notes that no BCF value for the test substance itself could be calculated from this method.

The analysis of the test fish revealed that the measured concentrations were below the limit of quantification in all samples (i.e. <0.25 mg/kg). Assuming that the limit of quantification represents the maximum concentration of the substance in fish, the equivalent BCF values can be estimated as <1300 for the group exposed to a concentration of 0.19 µg/L and <100 for the group exposed to 2.6 µg/L. ECHA considers that these results are not sufficient to support your conclusion that the BCF of the registered substance is below 100. They do not rule out either that the BCF could be >500.

The authors also analysed the fish from day 30 for the presence of total tin. The concentration of total tin present in the fish was found to be 0.027 mg Sn/kg for the 0.19 µg/L exposure group and 0.054 mg Sn/kg for the 0.26 µg/L treatment group. This method

[3] [redacted] (2010). Bioconcentration Test in Rainbow Trout with Dioctyltin Bis(2-Ethylhexyl Thioglycate) (Flow Through). Testing laboratory: [redacted]

is not specific for any given organotin compound as these values will represent the total tin concentration for all tin containing substances present in the samples, including any transformation products. No total tin analysis was carried out on the water concentration. In order to calculate the BCF, the authors converted the measured concentrations of DOT and MOT to the equivalent level of tin. The authors assumed that the percentage tin in DOT was 29.5% and the percentage tin in MOT was 37%, by mass. The total tin concentration in water was then estimated from the measured concentration of DOT and MOT by applying these percentages; the total tin concentration was the sum of tin from these two sources. In the case of MOT, as it was not quantifiable in water, the limit of quantification was used in the calculation. This led to total tin concentration of 0.15 µg Sn/L at the low exposure concentration and 0.92 µg Sn/L at the high exposure concentration. Using these concentrations, the BCF values based on total tin were 178 at the lower treatment group and 58 at the higher treatment group. However, this correction as applied in [redacted] (2010) is questionable[4]. The use of the limit of quantification for MOT may result in an overestimate of the total tin concentration in water (and hence an underestimate of the resulting BCF). It would be more appropriate to ignore here any contribution from MOT (particularly as the dioctyl tin substance tested had a purity of [redacted]). Furthermore, it may be more appropriate to use the percentage of tin in $DOT(EHTG)_2$ rather than the percentage of tin in DOT. The percentage of tin in $DOT(EHTG)_2$ is 15.8%, by mass. Taking into account these two factors, the revised total tin concentrations in test media would be estimated to be around 0.030 µg Sn/L at the low exposure concentration and 0.41 µg Sn/L at the high exposure concentration, compared to the concentrations of 0.15 µg Sn/L and 0.92 µg Sn/L as derived by [redacted] (2010). Comparing these concentrations with the measured total tin concentration in the fish (0.027 mg Sn/kg and 0.054 mg Sn/kg respectively) would lead to revised estimates for the BCF values based on total tin of around 900 at the low exposure concentration and 130 at the high exposure concentration. Again, ECHA notes that these results are not sufficient to support your conclusion that the BCF of the registered substance is below 100. They do not rule out either that the BCF could be >500.

Finally, ECHA notes that no time trend data on the actual concentration of the substance in the fish are reported in this study. Therefore, it is not possible to ascertain whether or not steady state was reached during the test. If no steady state had been reached, then the BCF values could have been further underestimated.

Therefore ECHA concludes that the available information does not rule out that the BCF for the registered substance is >500. Considering in addition that the registered substance is not rapidly biodegradable, and that under the endpoint study record in IUCLID section 4.7 in the technical dossier, the reported LogKow value is >6.5 for the registered substance, the classification of the substance as chronic aquatic toxicity as 'H413: May cause long lasting harmful effects to aquatic life' (Category Chronic 4) should be applied, unless a scientific justification is provided.

In your comments according to article 50(1) of the REACH Regulation, you agree that "as long there is no data on the substance itself available, based on the data on surrogate substances [classification for] H413: May cause long lasting harmful effects to aquatic life' (Category Chronic 4) should be warranted."

[4] see https://www.echa.europa.eu/documents/10162/13628/dichlorodioctylstannane_pbtfactsheet_en.pdf

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to provide adequate hazard classification and resulting hazard label for chronic aquatic toxicity for the registered substance subject to the present decision. In the alternative, you are required to provide scientifically justified reasons why no such classification is given.

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 the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 01 March 2017.

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

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and did not amend the requests.
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 during its MSC-63 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 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.

4. If the required tests are conducted with an analogue substance in the context of a read-across approach, the identity of the test material used to perform the test should be specified in line with ECHA's Practical Guide on "How to use alternatives to animal testing to fulfil your information requirements" (chapter 4.4). This is required to show that the test material is representative of the analogue substance identified in the read-across approach and used to predict the properties of the registered substance.