EUROPEAN CHEMICALS AGENCY

Helsinki, 30 May 2017

Addressee: [redacted]

Decision number: CCH-D-2114360967-34-01/F
Substance name: 2-ethylhexyl 10-ethyl-4-[[2-[(2-ethylhexyl)oxy]-2-oxoethyl]thio]-4-octyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate
EC number: 248-227-6
CAS number: 27107-89-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 18 January 2016
Tonnage band: > 1000 tpa

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. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rabbits), oral route with the registered substance;**

2. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance;**

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

It is at the Registrant's discretion to perform the intended additional examinations during the testing program;

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **7 December 2020**. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing, including time to perform the comet assay requested in another decision, which is the result of a testing proposal examination.

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

Appeal

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

Authorised[1] by 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

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(e) and 13(4) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of the REACH Regulation.

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

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The technical dossier contains information on a pre-natal developmental toxicity study in rats by the oral route using the registered substance as test material.

However, there is no information provided for a pre-natal developmental toxicity study in a second species.

You provided the following justification for the adaptation: *"A waiving for the prenatal developmental rabbit study (OECD 414) is proposed, because the OECD 421 study showed no effects on fertility and reproductive performance. Moreover, the results of the prenatal developmental rat study (OECD 414) showed no developmental toxicity even in the presence of maternal toxicity."* While you have not specified your adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2.

However, ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI; Section 1.2. because the information available in the dossier does not allow to assume or conclude that the registered substance has or has not a particular dangerous property, i.e. developmental toxicity. Specifically, there is information from two independent sources (studies) and ECHA notes that OECD TG 414 provides adequate information on first species and OECD TG 421 study could provide limited indirect information of developmental toxicity in form of reduced litter size. However, both studies are on the same species and, thus, cannot provide information on developmental toxicity on a second species. At the current Annex level, information on developmental toxicity in two species is required to conclude on property to cause the developmental toxicity. On the basis of these sources of information, considered either individually or together, ECHA cannot assume or conclude whether the substance subject to the present decision is a developmental toxicant or not. Therefore, your adaptation of the information requirement is rejected.

In your comments to the draft decision, you have proposed a Weight of Evidence adaptation, according to Annex XI, 1.2. This includes OECD 414 and 421 studies on the registered substance MOTE, and read-across studies from MOTC (an OECD 421 study), dioctyltin ethylhexyl thioglycolate (DOTE; OECD 414 studies on mouse and rabbit), and argument that dialkyl organotins are more toxic than monoalkyl organotins. You conclude that the requested study is highly unlikely to produce an adverse outcome.

You cite results from an OECD 414 and OECD 421 with MOTE and MOTC and the lack of developmental toxicity effects in these tests and argue that it can be used as part of your weight of evidence approach to justify not testing the second species.

ECHA considers that while these two studies may provide evidence that MOTE does not cause developmental toxicity in rats, no conclusion on potential non-rodent teratogenicity can be drawn.

You have proposed read-across to various alkyltin compounds. ECHA acknowledges that there is structural similarity, but notes that you have not provided a hypothesis to explain why the properties of the registered substance can be predicted from the properties of the source substance, for the source substances monooctyltin trichloride, monobutyltin chloride, dibutyltin chloride and DBTC. You have proposed that dialkyl tins are more toxic than monoalkyl tins, and so the results on DOTE can be read-across to MOTE. However, ECHA considers that this general assertion lacks experimental evidence and reasoning for the read-across from DOTE to MOTE. Specifically, there is no explanation why DOTE should be more toxic than MOTE. Accordingly, ECHA considers that the read-across does not meet the requirements of Annex XI, 1.5.

Further, regarding your reference to studies with DOTE in mice and rabbits, ECHA notes that the dossier for DOTE (synonyms: DOT(EHMA)2 and Dioctyltin bis(2-ethylhexyl mercaptoacetate) (EC Number: 239-622-4 CAS Number: 15571-58-1) has developmental toxicity studies (according to OECD 414) in rats ([redacted], 1991), mice ([redacted], 1992) and rabbits ([redacted], 2001). None of the studies were conducted on the DOTE. The studies used Dioctyltin bis(IOMA) [CAS no. 26401-97- 8]:Octyltin tris(IOMA) [CAS no. 26401-86-5] mixture (≥[redacted]:<[redacted]%) (one rat study, one study in rabbits, one study in mice). Since you are not reading across from DOTE, but rather from other substances, this is another reason why the read-across is rejected.

As an additional concern, in mice skeletal variations were significantly increased at dose levels (≥20 mg/kg bw/day) below those causing lower maternal thymus weight effects (45 and 100, but not 67 mg/kg bw/day) ([redacted] 2001). Significant increases of skeletal abnormalities were seen at ≥67 mg/kg bw/d while no other signs of maternal toxicity were recorded except decreased liver weight and one dead dam at 100 mg/kg bw/day. No significant maternal toxicity was present in rabbits at doses that caused abortions, fetolethality and skeletal /visceral abnormities [redacted], 1992). In conclusion, rabbit seems to be less sensitive to maternal (thymotoxicity) than rat, yet there were numerous developmental toxicity effects seen in rabbit, which were not present in the rat. There is thus concern for developmental toxicity from these studies on structurally related substances. This is a further reason for rejecting the read-across.

Due to these shortcomings, the studies cannot provide sufficient weight of evidence.

The test in the first species was carried out by using a rodent species (rats). According to the test method EU B.31/OECD 414, the rabbit is the preferred non-rodent species. On the basis of this default assumption, ECHA considers that the test should be performed with rabbits as a second species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

There is concern about the dose range applied in the available pre-natal developmental toxicity study in the first species rats. In particular, we would like to emphasize that organotin substances are known to have potential to cause not only thymic atrophy in maternal animals, but also other effects such as severe developmental effects in offspring. In the literature, there is evidence from structurally-related substances (i.e. organotins) showing increased incidence of dead or resorbed foetuses, external malformations and skeletal malformations starting at doses of organotin leading to substantial decrease in thymus weight and also leading to statistically significant decrease in body weight gain (thymus weight decrease of 50-60%; body weight gain decrease 20%[2]). This observation is also obvious from the WHO summary of the toxicological data of organotin compounds, in which the teratogenicity is observed at several-fold higher dose levels than the thymus effects[3]. We emphasize that minor changes in thymic weight (i.e. less than an 80% decrease in weight) on its own cannot justify the selection of the highest test dose. As set out above, it is necessary to dose structurally-related compounds (i.e. organotins) at a level which causes maternal toxicity in order to evaluate their developmental toxicity. ECHA considers that less than an 80% decrease in thymus weight is insufficient to demonstrate toxicity to the standard of this guideline, and so evidence of maternal toxicity is also required for the test to be conducted with the registered substance. Therefore, the doses for the pre-natal developmental toxicity study in the rabbit should be selected taking in account the existing toxicity data and the highest dose should be chosen with the aim to induce some developmental and /or maternal toxicity, i.e. clinical signs or a decrease in body weight, but not death or severe suffering. At least one intermediate dose level should produce minimal observable toxicity effects (OECD TG 414/ EU test method B.31).

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: EU B.31./OECD TG 414) in a second species rabbits by the oral route.

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. 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

In the technical dossier you have provided a study record for a OECD TG 421 "reproduction/developmental toxicity screening test" (2009). However, this study does not provide the information required by Annex X, Section 8.7.3. because it does not cover key elements, such as exposure duration, life stages and statistical power of an extended one-generation reproductive toxicity study.

[2] Noda, T., T. Yamano, M. Saitoh, T. Nakamura, and S. Morita. Comparative teratogenicity of di-n-butyltin diacetate with n-butyltin trichloride in rats. Arch Environ. Contam. Toxicol. 23, 216-222 (1992).
[3] WHO, 2006, Table 24

More specifically, the main missing key elements are: 10 weeks pre-mating exposure duration, at least 20 pregnant females per group, and an extensive postnatal evaluation of the F1 generation. In addition, there is a particular concern for developmental immunotoxicity according to column 2 of Annex X, Section 8.7.3. and information for those properties are missing. Therefore, the study record present in the registration dossier does not provide equivalent information to that from an extended one-generation reproduction toxicity study.

Hence, 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 Annex X, Section 8.7.3. is required. The following refers to the specifications of this required study.

b) The specifications for the study design

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, 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 4.1, October 2015). Ten weeks exposure duration is supported also by the lipophilicity of the substance to ensure that the steady state in parental animals has been reached before mating.

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

It is recommended that results from a range-finding study (or range finding studies) for the extended one-generation reproductive toxicity study 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 X.

ECHA notes that existing information on the registered substance itself derived from available *in vivo* studies show evidence of decreased thymus weights in the OECD TG 421 (2009) and OECD TG 414 (2014) studies, which suggests a concern for immunotoxicity. In the OECD TG 421 study, a decrease of absolute and relative thymus weight was observed in the 500 and 1250 mg/kg diet groups. In the summary of the OECD 414 it is stated: "*The mean absolute and relative thymus weights were decreased (>10 %) in the mid and high dose group. Immunotoxic compounds containing octyltin are known to affect thymus weight in pregnant/lactating females.*

Therefore, although the decrease in thymus weight in the mid and high dose group did not reach statistical significance, it was considered to be an adverse and test material-related effect." The substance seems to have sensitising properties which further supports immunotoxicity concern to trigger the immunotoxicity cohort.

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* studies.

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

Species and route selection

According to the test method EU B.56/ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, 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 4.1, October 2015) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.
In your comments, you express willingness to conduct the requested OECD 443.

You have proposed that a 2-week pre-mating exposure is sufficient, based on results from 90-day studies (including with read-across substances) and OECD 421/422 studies (presumably the OECD 221 study is a typographical error). However, ECHA's guidance states "There may be good quality information from existing repeated dose toxicity 90-day studies showing no effects in organ weights or histopathology of reproductive organs, and covering also the spermatogenesis and folliculogenesis. However, this information alone, or with the results from a screening study (OECD TGs 421 or 422) may not provide adequate confidence to shorten the premating exposure duration from ten weeks. This is because the information on mating and fertility from a screening study as well as the data from the repeated dose toxicity study is limited. Mating and fertility data from screening studies (OECD TGs 421 or 422) is after two weeks premating exposure duration not covering the full spermatogenesis and folliculogenesis and may also not be adequately long enough for detecting toxicity in hypothalamus-pituitary-gonad axis. In addition, the statistical power is low in these studies as they are not meant to provide comprehensive information on reproductive toxicity. Repeated dose toxicity 90-day studies may provide information on organ weights and histopathology but no mating data. The statistical power in the 90-day study is lower than that in the extended one-generation reproductive toxicity study also considering the data for histopathology. In addition, the exposure duration and exposure history are different in screening studies (OECD TGs 421 or 422) and 90-day studies. Thus, it may be difficult to conclude based on this information that a two-week premating exposure duration is sufficient for a substance in question." Appendix R.7.6–3 of Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7a: Endpoint specific guidance, Version 4.1, October 2015. These considerations also apply in this case. Hence, your proposal for a 2-week pre-mating exposure is rejected.

ECHA acknowledges your plans with regard to the dose selection.

EUROPEAN CHEMICALS AGENCY

You propose a design modification of the EOGRT study by adding two groups (designated 4B and 4C) to determine whether the effects are due to prenatal, gestational or postnatal exposure. It is at your discretion and responsibility to perform the intended additional examinations during the testing program. However, you must ensure that the conduct of the OECD 443 study, as detailed in the decision, is not impaired.

c) Outcome

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: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral route, according to the following study-design specifications:

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

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, 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 new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the new information shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Appendix 2: Procedural history

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 the previous lead under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 30 November 2015.

This decision is addressed to you because you have taken over the role of the joint submission's lead registrant from ARKEMA B.V on 18 January 2016.

You submitted comments to the draft decision on 29 January 2016.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation:

ECHA notified you of the draft decision and invited you to provide comments. ECHA took into account your comments, which were sent within the commenting period, and they are reflected in the Reasons (Appendix 1).

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

ECHA received proposal 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.

You did not provide any comments on the proposed amendment(s).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-53 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. The substance subject to the present decision is provisionally listed in the Community rolling action plan (CoRAP) for start of substance evaluation in 2019.

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

3. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

4. In relation to the information required by the present decision, the sample of the substance used for the new test(s) must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants. It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new test(s) is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new test(s) must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.