

Helsinki, 3 September 2018

Addressee: [REDACTED]

Decision number: CCH-D-2114440644-51-01/F  
Substance name: Trioctyl benzene-1,2,4-tricarboxylate  
EC number: 201-877-4  
CAS number: 89-04-3  
Registration number: [REDACTED]  
Submission number: [REDACTED]  
Submission date: 24/01/2018  
Registered tonnage band: Over 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. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance specified as follows:**
  - **At least two weeks pre-mating 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); and**
  - **Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation.**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI 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 **10 September 2020**. You also have to update the chemical safety report, where relevant.

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

The scope of this compliance check decision is limited to the standard information requirements of Annex X, Section(s) 8.7.3. to the REACH Regulation.

## **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<sup>1</sup> by Ofelia Bercaru, Head of Unit, Evaluation E3

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<sup>1</sup> 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****1. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)**

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

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. Further detailed guidance on study design and triggers is provided in the ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter 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*

In decision CCH-D-2114350062-64-01/F ECHA concluded, after evaluating the relevant information in your registration dossier, that an extended one-generation reproductive toxicity study according to Annex X, Section 8.7.3. is required. Indeed, in that decision it was indicated that 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 that same decision ECHA required you to provide a sub-chronic toxicity study (90-day). The decision indicated that the sub-chronic toxicity study shall be conducted before the extended one-generation reproductive toxicity study and the results from the 90-day study shall be used, among other relevant information, to decide on the study design of the extended one generation reproductive toxicity study.

In accordance with that decision you provided the results of a sub-chronic toxicity study.

*b) The specifications for the study design*

You did not provide any considerations of the study design.

Based on the experimental results submitted for the sub-chronic toxicity study (90-day), ECHA has re-evaluated the design of the EOGRT study and concluded that a new decision needs to be taken following the procedure under Articles 50 and 51 addressing the design of that study.

*Premating exposure duration and dose-level setting*

To ensure that the study design adequately addresses the fertility endpoint, the duration of the pre-mating 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 pre-mating 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 pre-mating exposure duration is required if there is no substance specific information in the dossier supporting shorter pre-mating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017). In this specific case, animals of Cohort 1B are mated to produce the F2 generation and, thus, the pre-mating exposure duration will be 10 weeks for these Cohort 1B animals and the fertility parameters will be covered allowing an evaluation of the full spectrum of effects on fertility in these animals. Thus, shorter pre-mating exposure duration for parental (P) animals may be considered. However, the pre-mating period shall not be shorter than two weeks and must be sufficiently long to reach a steady-state in reproductive organs as advised in the ECHA Guidance. The consideration should take into account whether the findings from P animals after a longer pre-mating exposure duration would provide important information for interpretation of the findings in F1 animals, e.g. when considering the potential developmental origin of such findings as explained in ECHA guidance.

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

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a conducted range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

#### *Extension of Cohort 1B*

If the column 2 conditions of 8.7.3., Annex X are met, Cohort 1B must be extended, which means that the F2 generation is produced by mating the Cohort 1B animals. This extension provides information also on the sexual function and fertility of the F1 animals. The extension is *inter alia* required, if the use of the registered substance is leading to significant exposure of consumers and professionals (column 2, first paragraph, lit. (a) of section 8.7.3., Annex X) and there are indications of one or more relevant modes of action related to endocrine disruption from available *in vivo* studies or non-animal approaches (column 2, first paragraph, lit. (b), third indent of section 8.7.3., Annex X).

The use of the registered substance in the joint submission is leading to significant exposure of consumers and professionals because the registered substance is used by consumers as lubricants and lubricant additives and there is consumer exposure to medical devices, building materials and car interiors (adult and children). Furthermore, the registered substance is used by professionals as lubricants and lubricant additives (PROCs 1, 2, 3, 4, 8a, 8b, 9, 10, 11, 13, 17, 18, 20, 28).

In your comments you state that there are no migration or release data available for the registered substance. Nevertheless, you agree that the exposure criterion is met.

Furthermore, the sub-chronic toxicity study (90-day) showed indications for endocrine-disrupting modes of action because changes in the absolute weight of a hormone-sensitive organ, uterus, was observed in females of all dose groups: -47% (low dose), -27% (mid dose) and -45% (high dose); the effect was statistically significant in low and high dose. ECHA notes that in females, the terminal body weights were max. 3% lower in treated animals compared to controls, and this can therefore not alone explain the above-mentioned decrease in uterus weight.

In your comments, you state that the change in uterus weights arises as a result of a clustering of high individual values within the control group and that the historical data on uterus weight shows high variability. ECHA notes that the individual data is not available in the robust study summary in the technical dossier, nor provided in your comments.

Furthermore, you have not shown that the high variability of historical control values is relevant for the results of this 90-day study as you have not provided any information on, for example, from which studies and during which period of time the control data was collected, and whether it was normalised for stage of oestrus cycle and size of animals. Hence, your statements cannot be confirmed.

ECHA concludes that Cohort 1B must be extended to include mating of the animals and production of the F2 generation because the uses of the registered substance is leading to significant exposure of professionals and consumers and there are indications of modes of action related to endocrine disruption from the available 90-day sub-chronic toxicity study (██████ 2017) for the registered substance.

#### *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 6.0, July 2017) R.7a, chapter R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

#### *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:

- At least two weeks pre-mating 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); and
- Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation.

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 pre-mating 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*

No triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including Cohorts 2A and 2B and/or Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the available information, together with 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* Chapter R.7a, Section 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.

**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.

On 14 December 2016 ECHA issued decision CCH-D-2114350062-64-01/F.

On 15 December 2017 the registrant provided a 90-day sub-chronic toxicity study.

On 12 February 2018 ECHA informed the registrant that the request for an EOGRT study was withdrawn and would be addressed in this separate decision.

The compliance check of the information requirement for an extended one-generation reproductive toxicity study was initiated on 2 February 2018.

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 amended the request(s).

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment.

As no amendments were proposed, ECHA took the decision according to Article 51(3) 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.