ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 29 October 2018

Addressee: [redacted]

Decision number: CCH-D-2114447795-35-01/F
Substance name: 2,4,6-tris(dimethylaminomethyl)phenol
EC number: 202-013-9
CAS number: 90-72-2
Registration number: [redacted]
Submission number: [redacted]
Submission date: 21/03/2018
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]

1. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **At least two 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) 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 **5 November 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

[1] No testing for endpoints listed in Annexes IX or X to the REACH Regulation may be started or performed at this moment: A decision only becomes legally effective and binding for you after it has been adopted according to Article 51 of the REACH Regulation. ECHA will take the decision either after the date it has become clear that Member State competent authorities have not made any proposals to amend the draft decision or, where proposals to amend it have been made, after the date the Member State Committee reached a unanimous agreement on the draft decision.

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[2] by Ofelia Bercaru, Head of Unit, Evaluation E3

[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

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 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-2114348335-49-01/F of 22 November 2016 ECHA concluded, after evaluating the relevant information in your registration dossier, that an extended one-generation reproductive toxicity study according 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 subchronic 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. Section 7.8.1 of the technical dossier refers to "*OECD Guideline 443 (Extended One-Generation Reproductive Toxicity Study)*" with a statement "*This information will be submitted after 2018-03 based on ECHA decision number CCH-D-2114348335-49-01/F.*"

b) The specifications for the study design

You have also provided your considerations of the study design, in light of the results of the provided 90-day study, proposing to conduct the basic test 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. ECHA does not agree with your conclusion on the basic study design. The reasoning for extension of Cohort 1B is given below.

In your comments you agree to provide an extended one-generation reproductive toxicity study. ECHA has taken into account your comments with justification that there is no particular concern for developmental neurotoxicity. Hence, the request for Cohorts 2A and 2B was removed from this decision.

Premating exposure duration and dose-level setting

Ten weeks premating exposure duration is required if 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 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 premating 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 premating exposure duration for parental (P) animals may be considered. However, the premating 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 premating 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 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 (Cf. OECD TG 443 para 21 & 22).

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 if 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 professionals as coatings, adhesives and composites by pump, roller, brush, spreader (PROCs 1, 3, 4, 5, 8a, 10, 11) and consumers as adhesives, sealants, coatings and paints, thinners, paint removes, fillers, putties, plasters and modeling clay.

Furthermore, the 90-day study showed indications for endocrine-disrupting modes of action because statistically significant changes in the absolute weights of hormone-sensitive organs such as prostate and seminal vesicles (-22%), ovaries (-27%) and uterus incl. cervix (-28%) in the high-dose test group (150 mg/kg bw/day) were observed. Even though the study report states that these findings were "*not considered to be test item-related but mostly caused by the reduced body weight in the high dose group*", ECHA notes that body weights were 12% (females) and 13% (males) lower compared to controls, and this can therefore not alone explain the above-mentioned reduction in organ weights.

In your comments, you indicate an intention to remove all consumer uses for the registered substance. Furthermore, you consider that also the professionals' exposure is very low. ECHA notes that even if all consumer uses were removed, the professional uses that are currently included in the dossier may still result in significant exposure for professional workers. There are many exposure scenarios for professional workers with PROCs (e.g. 5, 8a, 10, 11) which are relevant for exposure considerations.

A member state proposed an amendment as the use and exposure information currently included in the dossier is not consistent with the information that you have provided in your comments, and it should be clarified; and that this information is relevant for triggering the EOGRTS cohort. As a response, you repeated your argument that the expected exposure of professionals is low and that the substance is mixed with epoxy resin, becoming a permanent part of the resin and it cannot be released into the workplace and/or environment anymore. ECHA notes that you have not supported this argument in your comments with detailed explanations of the conditions and exposure scenarios, rate of reaction (of the registered substance or the matrix) and exposure estimates over time. In contrast, your exposure estimates in the provided CSR are describing relevant exposure, although you make the caveat that "*As the substance begins to cure immediately upon mixing, exposure risks decrease over time.*" In the absence of more specific information, ECHA cannot assume that the exposure of professionals is negligible.

In addition, you consider that the weight reduction on reproductive organs cannot be a primary effect, but that it is related to the vacuolization of arteries and smooth muscle cells, indicative of phospholipidosis. You also state that there were no specfic changes in oocytes or sperm cells. ECHA notes that the presumed phospholipidosis is anticipated to increase organ weights and hence it would not explain the reduction in the weights of these reproductive organs. The study report and the attached analysis ([redacted] 2018) do not mention any histopathological findings except the vacuoles; however, ECHA notes that the extensive vacuolization could have interfered with the histopathological analyses, and that >20% reduction in the absolute weights of these hormone-sensitive organs is of concern.

Furthermore, supporting the indication of an endocrine-disrupting mode of action, the analysis by [redacted] (2018) refers to a higher level of pre-implantation loss observed in a developmental study at 50 and 150 mg/kg/day. Taken together, ECHA maintains its opinion that the mentioned effects are indicative of mode(s) of action related to endocrine disruption.

Therefore, 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 repeated dose oral toxicity study (OECD TG 408, LPT 2017) for the registered substance.

Species and route selection

According to the test method 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 OECD TG 443), in rats, oral route, according to the following study-design specifications:

- At least two 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) 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 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

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.

Deadline to submit the requested information in this decision

In the draft decision communicated to you the time indicated to provide the requested information was 24 months from the date of adoption of the decision. In your comments on the draft decision, you did not request an extension of the timeline. In your comments on the Proposals for Amendment, you requested an extension of the timeline to 30 months. You sought to justify this request by arguing (1) the OECD 443 study requires higher efforts (2) it can be time consuming to select a test laboratory (3) you have to manage many OECD 443 studies. ECHA provides a standard time for the conduct and reporting of an OECD

443 study, which allows sufficient time. You have not provided specific reasoning, and supporting documentation, to explain why you need more time in your particular case. You have not provided reasoning nor evidence to explain why (1) the OECD 443 study requires higher efforts in your case (2) it should be more time-consuming for you to select a test laboratory (3) how many and which OECD 443 studies you have to manage, allied to an estimation of the time required for managing such studies, and a consideration of why this commitment of resources is inappropriate. Therefore, ECHA has not modified the deadline of the decision.

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 22 November 2016 ECHA issued decision CCH-D-2114348335-49-01/F.

On 29 November 2017 the registrant provided a 90-day sub-chronic toxicity study.

ECHA evaluated the results of this new study and concluded that it needs to re-initiate the compliance check of the information requirement for an extended one-generation reproductive toxicity study.

The compliance check of the information requirement for an extended one-generation reproductive toxicity study was initiated on 8 January 2018.

On 31 January 2018 ECHA informed the registrant that the request for an extended one-generation reproductive toxicity study in decision CCH-D-2114348335-49-01/F was withdrawn and would be addressed in this separate decision.

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.

ECHA received proposal for amendments and modified the draft decision.

ECHA invited you to comment on the proposed amendments.

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 in its MSC-61 written procedure 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.