~~Confidential~~

Helsinki, 09 December 2022

Addressees
Registrant(s) of K54-2010 as listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject to this decision
26/03/2021

Registered substance subject to this decision ("the Substance")
Substance name: 2,4,6-tris(dimethylaminomethyl)phenol
EC number: 202-013-9

Decision number: Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/F)

DECISION TAKEN UNDER ARTICLE 42(1) OF THE REACH REGULATION

By decision CCH-D-2114447795-35-01/F of 29 October 2018 ("the original decision") ECHA requested you to submit information by 5 November 2020 in an update of your registration dossier.

Based on Article 42(1) of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA examined the information you submitted with the registration update specified in the header above, and concludes that

Your registration still does not comply with the following information requirement:

A. Information required from all the Registrants subject to Annex X of REACH

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 are therefore still required to provide this information requested in the original decision.

Reasons for the request(s) are explained in the following Appendix A "Reasons to request information required under Annexes X of REACH".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

The respective Member State competent authority (MSCA) and National enforcement authority (NEA) will be informed of this decision. They have the duty under Articles 125 and 126 of Regulation No 1907/2006 to ensure that the requests in the original decision are enforced and complied with and, to that end, inter alia, to carry out checks and impose effective, proportionate and dissuasive penalties[1].

Authorised[2] under the authority of Mike Rasenberg, Director of Hazard Assessment

[1] See paragraph 143 of the judgment of the European Court of Justice of 21 January 2021 in Case C-471/18 P Germany v Esso Raffinage.

[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 A: Reasons to request information required under Annex X of REACH

1. Extended one-generation reproductive toxicity study

You were requested to submit information derived with the Substance for Extended one-generation reproductive toxicity (EOGRT) study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route with at least two weeks premating exposure, Cohorts 1A and 1B with extension to produce F2 generation and aiming to induce systemic toxicity at the highest dose level.

Information provided

In the updated registration subject to follow-up evaluation, you have provided an EOGRT study ([redacted] 2020) according to OECD TG 443.

Assessment of the information provided

We have assessed this information and identified the following issues:

To fulfil the information requirement, a study must comply with OECD TG 443 as specified in REACH (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) the key parameters for systemic toxicity are to be examined, including following investigations:
    a. Organs of Cohort 1B, all dose levels,
    b. Target organs in Cohort 1B and
    c. Organs of P0 and Cohort 1A animals at low and mid dose.

The objective of Cohort 1B is primarily to follow-up assessment of reproductive performance by mating F1 animals, when assessed (see GD 117 (39)), and for obtaining additional histopathology data in cases of suspected reproductive or endocrine toxicants, or when results from Cohort 1A are equivocal.

The study provided is described as a EOGRT study according to OECD TG 443.

However, the following specifications are not according to the requirements of the OECD TG 443:

b) the systemic toxicity was not fully investigated, in particular, the following investigations are missing:
    a. Organs of Cohort 1B, all dose levels,
    b. Target organs in Cohort 1B (only liver and spleen were preserved) and
    c. Organs of P0 and Cohort 1A animals at low and mid dose.

In this case, the extension of Cohort 1B was triggered to address a concern for endocrine-disrupting modes of action. Therefore, reproductive and endocrine tissues from all cohort 1B animals, processed to the block stage (OECD TG 443, paragraph 67), should have been examined for histopathology as in cases of suspected reproductive or endocrine toxicants. Furthermore, organs and tissues demonstrating treatment-related changes in high dose animals and all gross lesions should also have been examined in all animals in the lower dose groups to aid in determining a NOAEL.

In the study you have provided histopathology was not investigated in Cohort 1B animals (all dose levels) for organs listed in OECD TG 443 paragraph 67 as you have reported histopathological investigations only for high dose and control animals of P0 and Cohort 1A. Therefore, based on the provided information, a reliable NOAEL value for organ toxicity cannot be derived because the histopathology of organs showing vacuolation or vacuolar changes in

smooth muscle cells/fibers of several organs at the highest dose level were not investigated at mid and low dose levels in P0 and Cohort 1A (OECD TG 443, paragraphs 70 and 71).

In your comments on the draft decision, regarding the missing items a. and b. you state that *Histopathological examinations of organs in Cohort 1 B only have to be performed if there are equivocal effects in the organs of Cohort 1 A animals.* However, the trigger to perform histopathological examinations in Cohort 1B is not only based of equivocal effects in Cohort 1A animals but also applicable based on the original concern of triggering the extension of Cohort 1B as explained in the original decision. As stated above, in this case the extension of Cohort 1B was triggered based on a concern for endocrine-disrupting modes of action in the OECD TG 408 study (2018) and this justifies the histopathological investigations of reproductive and endocrine tissues from all Cohort 1B animals. The importance of Cohort 1B animals is justified with longer exposure duration compared to Cohort 1A animals and therefore effects may be seen at lower dose levels.

As regards missing investigations for organs of P0 and Cohort 1A animals at low and mid dose you seek to highlight in your comments on the draft decision that the effects occurring in several organs of Cohort 1A and the parental generation are the same as observed in the 90-day repeat-dose toxicity study (2018). In that study the same dose groups were used as in the subsequently performed OECD TG 443 study, and histopathological investigations were then performed in various organs in the intermediate and the low dose groups. You summarized that the histopathological examination revealed that the test item induces systemic vacuolation considered to be associated with phospholipidosis, not only in F0 generation animals but also in F1 generation animals. You further explain that the re-evaluation of the vacuoles noted in the 90-day study using electron microscopy evaluation ([redacted] 2018) revealed the presence of membrane bound vacuoles which was indicative for lysosome containing myelin figures, and hence is to be not relevant for human health. You consider that the organ weight changes recorded in the EOGRTS study (OECD TG 443) were of less or no toxicological significance, and the vacuolations observed were qualitatively the same between generations. You conclude that further examination of the systemic effect 'phospholipidosis' of the same dose groups of the same organs seem redundant. ECHA notes that the impact of study design, namely pregnant animals and inclusion of filial generation even if exposed to same dose groups, makes the EOGRTS more informative regarding more sensitive life stages. The aim is to investigate also mid dose and low dose animals to confirm no/lowest observed adverse effects level (NOAEL/LOAEL) for classification and labelling purposes, derived no-effect level (DNEL) derivation and risk assessment (see Section 1.0.1 of Annex I, REACH).

ECHA considers that the possibility to set LOAEL instead of NOAEL at lowest dose level is relevant justification to investigate low and mid dose histopathology. Finally, ECHA notes that relevance to humans of the vacuolisation cannot be ruled out and it could be considered as adverse especially when critical organs (such as brain/heart/lungs) are affected. ECHA consideres that your approach does not allow setting a reliable LOAEL/NOAEL for organ toxicity based on the EOGRTS study in consideration of differences in exposure period and more sensitive life stages.

In summary, you have not provided the histopathological investigations of 1) Organs of Cohort 1B, all dose levels, 2) Target organs in Cohort 1B (only liver and spleen were preserved) and 3) Organs of P0 and Cohort 1A animals at low and mid dose.

On this basis, the request in the original decision was not met and the information requirement is not fulfilled.

Therefore, pursuant to Article 42(1) of the REACH Regulation, you are still 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.

Appendix B: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[3].

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. Selection of the Test material(s)

   The Test Material used to generate the new data must be selected taking into account the following:
   - the variation in compositions reported by all members of the joint submission,
   - the boundary composition(s) of the Substance,
   - the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

2. Information on the Test Material needed in the updated dossier
   - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[4].

[3] https://echa.europa.eu/practical-guides
[4] https://echa.europa.eu/manuals

Appendix C: Procedure

In accordance with Article 42(1) of the REACH Regulation, the Agency examined the information submitted by you in consequence of decision of 29 October 2018 ("the original decision"). The Agency considered that this information did not meet one or more of the requests contained in that decision. Therefore, a new decision-making process was initiated under Article 41 of the REACH Regulation.

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

ECHA followed the procedure detailed in Articles 50 and 51 of REACH, 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.

You also commented on the missing deadline for submitting the information. In this respect ECHA notes that this decision does not give a new deadline as the information requested has not changed.[5] You must still comply with the information requirements set out in the original decision.

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

[5] This point was confirmed by ECHA's Board of Appeal in its decision in case A-001-2019.

Appendix D: List of references - ECHA Guidance[6] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[7]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[8]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

[6] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[6] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[7] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[8] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316

OECD Guidance documents[9]
Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

[9] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix E: Addressees of this decision and the corresponding information requirements applicable to them

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.