EUROPEAN CHEMICALS AGENCY

Helsinki, 22 July 2019

Addressee: [redacted]

Decision number: CCH-D-2114476402-51-01/F
Substance name: Ethanol, 2,2'-oxybis-, reaction products with ammonia, morpholine derivs. residues
EC number: 272-712-1
CAS number: 68909-77-3
Registration number: [redacted]
Submission number: [redacted]
Submission date: 25/09/2018
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 OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **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); and**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.**

You have to submit the requested information in an updated registration dossier by ***29 July 2021***. You shall also 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[1] by Ofelia Bercaru, Head of Unit, Hazard Assessment

[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

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[2].

In Decision CCH-D-2114352349-44-01/F 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 requested 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 have provided the results of a sub-chronic toxicity study (90-day). In light of these results, you also provided your considerations of the design of the extended one-generation reproductive toxicity study, proposing "*extended one-generation reproductive toxicity - basic test design (Cohorts 1A, and 1B without extension)*".

Based on the experimental results submitted for the sub-chronic toxicity study (90-day), ECHA and the Member State authorities have re-evaluated the design of the extended one-generation reproductive toxicity study.

Two Member States authorities considered that there was a need to include Cohorts 2A and 2B in particular based on the following findings, which were already indicated in their proposals for amendment during decision-making for CCH-D-2114352349-44-01/F:

- Constituents (ethylene glycol (ethane-1,2-diol): [redacted] and diethylene glycol (or 2,2'-oxydiethanol): [redacted] of the registered UVCB substance showing neurological effects:
    - human poisoning case reports
    - glycol ethers displaying potent activity for estrogen and androgen receptors

[2] ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017)

  - ethylene glycol showing effects on the estrogen system of rainbow trout
- Further strengthened by an observation from the sub-chronic toxicity study (90-day) for the registered substance: "*the behavioural assessment of the 90 day study, showing that the final 20% of activity was statistically significantly lower ($p<0.05$) than controls for all treated males*"

In your comments you consider that there is no need to conduct Cohorts 2A/2B. You acknowledge that two constituents of the registered substance, namely ethylene glycol (ethane-1,2-diol) and diethylene glycol (2,2'-oxydiethanol) have neurological effects but you emphasize that the newly-provided OECD TG 408 study, conducted with the registered UVCB substance, did not show neurotoxic effects. Furthermore, you explained that the change in the final 20% activity reported in the OECD TG 408 study is taken out of context: it is only one of several parameters evaluated for functional performance, and the overall analysis demonstrates that there were no treatment-related effects in functional performance.

Two Member State authorities also considered that Cohort 3 should be included in particular based on the following findings which were already indicated in their proposals for amendment during decision-making for CCH-D-2114352349-44-01/F:

- Constituents (ethylene glycol (ethane-1,2-diol): [redacted] and diethylene glycol (or 2,2'-oxydiethanol): [redacted] of the registered UVCB substance showing immunological effects:
  - mouse acute poisoning study with ethylene glycol
  - ethylene glycol acts on T and B lymphocytes *in vitro*
  - glycol ethers displaying potent activity for estrogen and androgen receptors
- Furthermore, the registered substance is "*self-classified as skin-sensitiser by most registrants*"

In your comments you consider that there is no need to conduct Cohort 3. You acknowledge that two constituents of the registered substance, namely ethylene glycol (ethane-1,2-diol) and diethylene glycol (2,2'-oxydiethanol), have immunological effects but emphasize that the existing OECD TG 421, 408 and 406 studies, conducted with the registered UVCB substance, have not shown endocrine disruption or immunological effects.
As some Member State authorities considered that the study design of the extended one-generation reproductive toxicity study needs to be revised, a new decision making process under Articles 50 and 51 of the REACH Regulation has to be followed for this information requirement, which would allow consultation and endorsement of all Member States.

In your comments you agree not to include extension of Cohort 1B. Furthermore, you indicate your agreement to include Cohort 1A but consider that in the absence of extension of Cohort 1B, "*the information acquired from Cohort 1B will be the same information as obtained in Cohort 1A (i.e., effects observed at weaning or at sexual maturation) and would therefore be redundant*". ECHA-S notes that, as explained in OECD TG 443, both Cohorts 1A and 1B are needed to inform on reproductive/developmental toxicity, and therefore both Cohorts 1A and 1B are requested in the decision.

In addition, in your comments you acknowledge that there is no need to assign a termination time for the F2 generation since extension of Cohort 1B is not requested. ECHA-S agrees.

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[3].

In your comments you agree to ten weeks premating exposure.

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 relevant data to be used for dose level setting, it is recommended that a range-finding study (or range finding studies) is performed and that its results are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

In your comments, you propose to base the dose-level selection on the existing repeated dose studies, i.e. the OECD TG 421 and 408 studies, and to use the "limit dose" of 1000 mg/kg bw/day as the highest dose, even if this dose level did not cause adverse toxicity in the above-mentioned studies. ECHA agrees that as per OECD TG 443, the highest dose level can be set to the limit dose of 1000 mg/kg bw/day, unless human exposure indicates the need for a higher dose level.

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[3], 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.

In your comments you agree to perform an OECD TG 443 study in rats, via oral route.

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:

- 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); and
- Cohort 1B (Reproductive toxicity) without 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

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) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, 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[3]. 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 31 January 2017 ECHA issued decision CCH-D-2114352349-44-01/F.

On 31 August 2018 the registrant provided a 90-day sub-chronic toxicity study.

On 4 October 2018 ECHA consulted the Member State authorities asking for their opinion whether the design of the extended one-generation reproductive toxicity study requested in decision CCH-D-2114352349-44-01/F should be revised. Two Member States informed ECHA that the design of the extended one-generation reproductive toxicity study needed to be reviewed.

On 29 November 2018 ECHA therefore informed the registrant that the request for an extended one-generation reproductive toxicity study in decision CCH-D-2114352349-44-01/F 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 26 November 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 did not amend the request(s).

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

ECHA received proposal(s) for amendment and did not modify 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.

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-65 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 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.