EUROPEAN CHEMICALS AGENCY

Helsinki, 10 April 2019

Addressee: [redacted]

Decision number: TPE-D-2114465873-37-01/F
Substance name: Tetrahydrothiophene 1,1-dioxide
EC number: 204-783-1
CAS number: 126-33-0
Registration number: [redacted]
Submission number: [redacted]
Submission date: 19/07/2018
Registered tonnage band: 100-1000

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation ((EC) No 1907/2006) (the REACH Regulation), ECHA examined your testing proposal(s) and decided as follows.

Your testing proposal is modified and you are requested to carry out:

1. **Extended one-generation reproductive toxicity study (Annex IX, 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);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation; and**
   - **Cohort 3 (Developmental immunotoxicity)**

You have to submit the requested information in an updated registration dossier by **19 April 2021**. You also have to update the chemical safety report, where relevant.

The reasons for 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.

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 C4

[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

The decision of ECHA is based on the examination of the testing proposal you submitted.

1. Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.)

Pursuant to Article 40(3)(b) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test under modified conditions.

The basic test design of an extended one-generation reproductive toxicity study (Cohorts 1A and 1B, without extension of Cohort B to include an F2 generation, and without Cohorts 2A, 2 B and 3) is a standard information requirement as laid down in column 1 of Section 8.7.3., Annex IX of the REACH Regulation if the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD TGs 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity, whereas column 2 defines when the study design needs to be expanded.

The following adverse effects on reproductive organs or tissues and other concerns in relation with reproductive toxicity are observed in the screening study with the registered substance (OECD TG 421, GLP, [redacted], 1999):

- Significantly reduced number of oestrus cycles during pre-mating period; you reported remaining uncertainties regarding the origin and relevance of reduced numbers of oestrus cycles, as reduced feed consumption and body weight gain which were also reported for those rats, might have had an impact on fertility.
- Significantly increased relative ovarian weights at necropsy in the high dose group (while absolute ovarian weights were 14.6% higher than in the control group).
- In the high-dose group, significantly decreased birth index, live birth index, number of live pups on lactation day 4, pup weights on lactation days 0 and 4 ($p < 0.01$), and viability index and significant increase in the number of stillbirths ($p < 0.01$) as well as total litter loss during lactation for four dams (US Environmental Protection Agency, 2012[2]).
- In the medium high dose group, significant decrease of birth index ($p < 0.05$) ($p < 0.05$; US Environmental Protection Agency, 2012[3]).

Nonetheless ECHA reminds you that it is your responsibility to ensure that testing on vertebrate animals shall be conducted only as the last resort according to Article 25 of the REACH Regulation. The study does not have to be conducted if the substance meets the criteria for the classification as toxic for reproduction (Cat 1A or 1B) and available data are adequate to support robust risk assessment.

ECHA notes that you proposed to conduct an extended one-generation reproductive toxicity study for a purpose to "*characterize the reproductive toxicity potential of sulfolane for classification purposes*", as you expressed some doubts on the reliability of the fertility data obtained in the above-mentioned screening study (OECD TG 421, [redacted] 1999). You therefore proposed that "*a more definitive study is required to adequately determined the reproductive toxicity potential and thus classification of sulfolane*". ECHA agrees with your proposal.
As the condition of Annex IX, Section 8.7.3. is fulfilled, an extended one-generation reproductive toxicity study is an information requirement for the registered substance pursuant to Annex IX, Section 8.7.3. The information on this endpoint is not available for

[2] https://cfpub.epa.gov/ncea/pprtv/documents/Sulfolane.pdf

the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

You have submitted a testing proposal for an extended one-generation reproductive toxicity study according to OECD TG 443 by the oral route in the rat, to be performed with the registered substance, according to the basic study design (10 weeks of premating exposure or two weeks if an extension of Cohort 1B is included and with a possible extension of Cohort 1B to produce an F2 generation, depending on the test results).

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (extended one-generation reproductive toxicity study). ECHA notes that you provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

The following refers to the specifications for the study design (premating exposure duration, dose level setting, expansions, species and route selection).

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[3], 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.

You proposed that pre-mating exposure duration shall be ten weeks or "*two weeks if an extension of Cohort 1B is included*". ECHA agrees that ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration and an extension of Cohort 1B is not required.

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.

Species and route selection

You proposed testing in rats and by the oral route. According to the test method OECD TG 443, the rat is the preferred species. On the basis of this default consideration, ECHA considers that testing should be performed in rats. ECHA agrees that the oral route is the most appropriate route of administration, since the substance to be tested is a liquid.

Cohort 3

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

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity as described in column 2 of Section 8.7.3., Annex IX. However you did not propose to include the Cohort 3 as you considered that "*there is no concern on immunotoxicity*."

Existing *in vivo* data on the registered substance contradicts this statement by showing the following evidence of immunotoxic effects:

- key sub-chronic oral toxicity study (OECD 408, GLP, [redacted], 2001), conducted with the registered substance:
  - statistically significant decreased in total white blood cells, lymphocyte, monocyte, basophil and large unstained cell counts in female rats compared with controls in the 10.6, 42.0 and 191.1 mg/kg bw/day groups.
  - body weight reduction or other toxicities were not observed at the termination and the changes in number of blood cells were dose-related.

- several other studies reviewed and summarised in the provisional peer-reviewed toxicity values report for sulfolane (US Environmental Protection Agency, 2012[4]):
  - immunotoxic effects of the registered substance (decreased white blood cells count, reduced spleen weight, shrinkage of the white pulp in the spleen).

Also you have identified the immune system as a target organ for the registered substance in the above-mentioned sub-chronic toxicity study. As a consequence, you have established a LOAEL of 10.6 mg/kg bw/day and a NOAEL of 2.9 mg/kg bw/day "*based on reduced immunological parameters in females*".

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* study on the registered substance.

Outcome

In your comments to the draft decision, you confirmed your intention to perform the proposed test and noted that this information might be used for clarifying your current self-classification and a concern on fertility. You also expressed doubts whether including an additional Cohort 3 would provide more relevant information on (potential) immunotoxicity of the registered substance. ECHA notes that, as outlined above, the developmental immunotoxicity Cohort 3 needs to be included in the EOGRTS design in case of a particular concern on (developmental) immunotoxicity. Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, you are requested to carry out the modified study with the registered substance, as specified above.

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 and/or Cohorts 2A and 2B 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 IX and further elaborated

[4] https://cfpub.epa.gov/ncea/pprtv/documents/Sulfolane.pdf

in ECHA Guidance[5]. 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.

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

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 22 November 2017.

ECHA held a third party consultation for the testing proposals from 23 April 2018 until 7 June 2018. ECHA did not receive information from third parties.

This decision does not take into account any updates after **10 December 2018**, 30 calendar days after the end of the commenting period.

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.

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 decision does not imply that the information provided in your registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the 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 the Member States.

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.