ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 10 April 2019

Addressee: [redacted]

Decision number: TPE-D-2114465809-32-01/F
Substance name: Sulphamidic acid
EC number: 226-218-8
CAS number: 5329-14-6
Registration number: [redacted]
Submission number: [redacted]
Submission date: 05/03/2018
Registered tonnage band: Over 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.

While your originally proposed test for Extended one-generation reproductive toxicity study in rats (OECD TG 443) using the analogue substance sodium sulphamate is rejected, you are requested to perform

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 **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 and scientific information submitted by third parties.

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

a) Examination of the testing proposal

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

The basic test design of an extended one-generation reproductive toxicity study (EOGRTS) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X of the REACH Regulation, whereas column 2 defines when the study design needs to be expanded.

The information on this endpoint is not available for 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 EOGRTS according to OECD TG 443 by the oral route in rats with 2-week premating exposure duration. You have provided the following justification, according to the criteria described in column 2 of Section 8.7.3 of Annex X and detailed in ECHA Guidance[2]: *"rats as preferred species are proposed and dosing of ammonium sulphamate as surrogate for the very acidic sulphamidic acid via feed is proposed";* and *"Oral exposure (via feed) is suggested as dermal and inhalation exposure are not very relevant and oral exposure provides the best chance for absorption also providing comparable data with other compounds. Any amendments by additional modules (neurotoxicity or immunotoxicity) or additional cohorts do not appear appropriate, as neither such effects are expected and no information on such effects have become known, following decades of continuous use in high tonnages."*

You have provided further justifications on e.g. exclusion of additional cohorts in an attached document.

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.

ECHA has evaluated your testing proposal, and could not ascertain which testing material you wish to use. On one hand you defined the test material as *"sulfamic acid / 5329-14-6 / 226-218-8"*, and specified that *"sodium sulphamate, the neutralized form as a surrogate"* would be tested. One the other hand, you also referred to ammonium sulphamate in the attached document and the justification (see above). You further explained that the *"toxicological effects seen may be solely attributable to low pH of the substance (strong acid) and thus application of ammonium salt (neutralized sulphamidic acid) is proposed for conducting the study."*

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

ECHA understands that you propose to generate data on an analogue substance to fulfil standard information requirements for this endpoint. Annex XI, Section 1.5 of the REACH Regulation sets out the provisions under which human health effects and environmental effects or environmental fate of a substance may be predicted from data obtained on a different substance and defines such an adaptation as grouping of substances and read-across.

According to Annex XI, Section 1.5. there needs to be structural similarity among the substances within a group or category and furthermore, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). Furthermore, Annex XI, Section 1.5. lists several additional requirements one of which is that adequate and reliable documentation of the applied method have to be provided.

You have not provided any read-across justification apart from referring to the low pH of the substance. However, ECHA notes that the dossier contains studies, e.g. two 105-day feeding studies (Ambrose, 1943) conducted with respectively sulphamidic acid and ammonium sulphamate (neutralized sulphamidic acid) with equivalent doses: both studies showed similar effects (i.e. a reduction in growth rate) and both NOAELs were set to 600 mg/kg bw/day. Furthermore, the dossier contains studies, such as a sub-chronic toxicity study (90-day; 1984) and a pre-natal developmental toxicity study (2014), conducted with the registered substance. Hence, ECHA considers that you failed to justify your read-across approach and that testing on the registered substance is not causing excessive toxicity preventing its use as testing material.

Therefore, ECHA concludes that an EOGRTS according to column 1 of Section 8.7.3., Annex X is required, using the registered substance, with your proposed study design and a modification on premating exposure duration.

In your comments, you agreed to perform the study with the registered substance, and you agreed to the requested study design and premating exposure duration.

The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

You proposed *"Premating exposure duration for parental (P0) animals : according to OECD443 2 weeks during pre-mating (males and females)"*.

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].

Therefore, the requested premating exposure duration is ten weeks.

Furthermore, you proposed that the dose level selections is "*based on a 14 days range finding study if exposure via feed*". ECHA agrees with your proposal.

In your comments, you proposed to apply the test substance via gavage, and use an existing dose-range-finding study (gavage) to set the dose levels. ECHA agrees that existing data can be used as a starting point for dose level setting. ECHA further emphasises that when setting dose levels, you should take into consideration all available data, and the test guideline requirements on dose level setting.

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 by oral route (via feed) in rats. ECHA agrees with your proposal.

In your comments, you agreed to perform the study "*as a per oralis study*", but you proposed to apply the test substance via gavage. Based on the available studies, ECHA agrees that the test substance can be administered via gavage.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

The third party provided their considerations of the test material and the study design for EOGRTS. The third party stated that "*the proposed read-across is supported in order to avoid testing with the acid*" and that the basic study design (Cohorts 1A and 1B without extension) "*is considered to be appropriate in the absence of any triggers or conditions necessitating the inclusion of additional cohorts or a further generation*".

ECHA acknowledges that the third party has proposed a read across / weight of evidence approach. For the read-across, the third party did not provide any further arguments and hence ECHA notes that this approach has been discussed above in section "a) Examination of the testing proposal".

Furthermore, the third party has commented that "*the Registration Dossier includes an older 3-generation reproductive toxicity study performed in the rat with ammonium sulphamidate. This study does not identify any effects on fertility or reproduction at any dose level tested. Although somewhat limited in design, the study confirms the lack of potential for reproductive toxicity seen for sulphamidic acid and its salts, as indicated by the NOAEL of 1000 mg/kg bw/d in an OECD 422 screening study with sodium sulphamidate. It may be possible to meet the data requirement through a weight of evidence approach using data available for the salts.*"

ECHA considers that the studies mentioned by the third party do not provide a sufficient basis for a weight of evidence approach because they do not cover key parameters, life stages and statistical power of an EOGRTS. In particular, the main missing elements are adequate histopathological examinations (especially of reproductive organs), the extensive postnatal evaluation of the F1 generation and less than 20 pregnant females per dose group. Furthermore, the 3-generation study was conducted with only two dose groups in addition to control group.

ECHA notes that it is your responsibility to consider and justify any adaptation of the information requirements in accordance with the relevant conditions as established in Annex XI, Sections 1.2 and 1.5. Therefore, you may assess whether you can justify a read-across or weight of evidence approach as suggested by the third party. If the information requirement can be met by way of adaptation, you may include the adaptation argument with all necessary documentation according to Annex XI, Section 1.2 or 1.5 in the updated registration dossier.

ECHA notes that the third party did not provide any additional scientific data which would fulfil this information requirement. Therefore, the information provided by the third party in itself is not sufficient to adapt the standard information requirement.

c) Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, you are requested to carry out the additional study with the registered substance, as specified above, while your originally proposed test for Extended one-generation reproductive toxicity study (OECD TG 443) with the analogue substance (sodium sulphamate) is rejected according to Article 40(3)(d) of the REACH Regulation.

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 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

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 6 March 2018.

ECHA held a third party consultation for the testing proposals from 23 April 2018 until 7 June 2018. ECHA received information from third parties (see Appendix 1).

This decision does not take into account any updates after **5 November 2018**, 30 calendar days after the end of the commenting period.

ECHA notified you of the draft decision and invited you to provide comments. An extension to the registrants commenting period on the draft decision was provided.

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.

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.