Helsinki, 5 April 2019

Addressee: [redacted]

Decision number: TPE-D-2114465815-39-01/F
Substance name: 2,5-Furandione, dihydro-, mono-C15-20-alkenyl derivs.
EC number: 272-221-2
CAS number: 68784-12-3
Registration number: [redacted]
Submission number: [redacted]
Submission date: 21/11/2017
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.

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

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 **12 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 proposals 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)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

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 Section 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 to be performed with the registered substance. 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]: *"Basic test design with default premating and dosing periods is proposed in the absence of any valid triggers for extension to F2 or cohorts 2 or 3. None of the criteria from E2-4, N1-3 nor I1-3 were met in order to trigger the additional cohorts."*

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (extended one-generation reproductive toxicity study). 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 concludes that an EOGRTS according to column 1 of Section 8.7.3., Annex X is required with your proposed study design with further specifications for premating exposure duration, species, and route of exposure.

In your comments you agreed to perform the requested study.

The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

You proposed *"default premating and dosing periods"*. ECHA understands that this proposal refers to the ECHA Guidance[3].

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]. Ten weeks exposure duration is supported also by the lipophilicity of the

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

substance ($logK_{ow}$ = 6.74 at 25 °C) to ensure that the steady state in parental animals has been reached before mating.

Therefore, the requested premating exposure duration is ten weeks.

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 proposed to conduct a dose-range finding study before initiating the main EOGRT study. ECHA agrees with your proposal since any pre-study can be conducted at your discretion.

Species and route selection

You did not specify either the route or the species to be tested. ECHA considers that the oral route is the most appropriate route of administration, since the substance to be tested is a liquid, and according to the test method OECD TG 443, the rat is the preferred species.

Therefore testing should be performed in rats, by oral route.

In your comments, you proposed to test Wistar rats, and to administer the test substance via oral gavage route. Based on the available data (OECD TGs 408, 422 and 414 studies provided in the dossier), ECHA agrees to these specifications.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation. The third party provided their considerations of the study design and stated 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*". However, the third party did not provide any scientific data which would fulfil this information requirement.

c) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed 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) 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 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.

In your comments you indicated that "*The addtion of internal triggers to enable transatlantic applicability of the study may still be considered based on the business needs of the registrants and to avoid unneccessary repetition of animal experiments.*" ECHA notes that, as explained above, you may expand the study, but the justification for the expansion must be documented.

ECHA notes that, as part of the testing proposal for EOGRTS, you also proposed experiments to "*investigate the lack of maternal care / lactation. The proposed investigations include in an additional satellite group the exchange of offspring from treated females with those of untreated females and vice versa.*"

ECHA understands that this proposal is based on the findings in the OECD TG 422 study showing insufficient maternal care at all dose levels, correlating with increased pup mortality. The study report states that "*The cause for the insufficent maternal care is presently undecided as the effect may be due to systemic maternal toxicity or due to an effect on the pups via lactation.*"

The OECD GD 43 (Guidance document on mammalian reproductive toxicity testing and assessment) foresees the advantages of cross-fostering experiments in certain circumstances (see paragraph 78). ECHA notes that you proposed to include an additional satellite group for cross-fostering without any further specifications on e.g. the number of animals, dose levels, termination time, or investigations to be performed.

ECHA considers that the highest dose level used in EOGRTS should be used for the cross-fostering investigations and that a group size equal to that used in OECD TG 422 should suffice. As the maternal care continues only up to weaning, ECHA considers that the satellite group should be treated in a similar way than the main study but can be terminated at the weaning. ECHA understands that the investigations proposed are focusing at least on mortality, growth and general health of the offspring and the dams. ECHA notes that using cross-fostering investigations it may not be possible to clarify whether pup mortality could be due to maternal toxicity or due to effects on the pups via lactation unless specific investigations such as excretion of the registered substance to the milk is conducted. ECHA considers that it is sufficient to investigate whether the pup mortality is linked to insufficient maternal care.

ECHA understands that you intend to include an additonal satellite group as described above and emphasises that it is your responsibilty to ensure that this addition does not compromise the requested EOGRT study design.

In your comments you proposed to conduct the cross-fostering study separately. ECHA agrees with your proposal of a separate study. As the cross-fostering study is aiming to bring additional information, not required in standard information requirement, you can freely select an appropriate study design. However, ECHA considers that in order to ensure findings which are in line with the OECD TG 422 study, the cross-fostering study should be conducted in a similar way in terms of exposure duration, dose levels and route of administration as well as other conditions.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 21 November 2017.

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 2 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.

In your comments you agreed to the draft decision. ECHA took your comments into account 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.