EUROPEAN CHEMICALS AGENCY

Helsinki, 21 August 2018

Addressee: [redacted]

Decision number: CCH-D-2114440661-55-01/F
Substance name: 2-[(2-methyl-1-oxoallyl)oxy]ethyl acetoacetate
EC number: 244-311-1
CAS number: 21282-97-3
Registration number: [redacted]
Submission number: [redacted]
Submission date: 23/03/2017
Registered tonnage band: 100-1000

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. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH Regulation. To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by ***28 August 2019***. You also have to 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.

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 Kevin Pollard, Head of Unit, Evaluation E1

[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

TOXICOLOGICAL INFORMATION

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement by providing the following justification:

"The developmental toxicity study requirement according to REACH Annex IX, section 8.7 was waived as the substance did not show any toxicological activity in the available tests. A subchronic oral toxicity study in the rat was performed according to OECD Guideline 408. The results of this oral gavage study indicate that the test item has no potential to produce toxic effects when administered to rats at dosage of 500 mg/kg/day.
*Based on the lack of treatment-related effects in clinical signs, ophthalmic examinations, feed consumption, weight gain, clinical pathology, organ weights, gross pathology, microscopic pathology, and FOB results, the no-observed-effect level (NOEL) for subchronic exposure to AAEM (*a synonym of the name of registered substance*) was considered to be 500 mg/kg/day for both male and female rats when administered 5 days per week for 13 weeks. The toxic potential of LZ649 (*the registered substance*) on basic reproductive processes was assessed in a OECD 421 screening study in which rats were dosed for two weeks prior to pairing, throughout gestation and lactation at dose levels of 50, 150 or 500 mg/kg/day. There was no adverse effect of administration with LZ649 on clinical condition, bodyweight, and food consumption, macroscopic and microscopic appearance. Reproductive performance assessments of oestrous cycles, gestation length and parturition for F0 females also showed no test article related change. Organ weights for F0 males were similar throughout the groups. The clinical condition, litter size and survival and sex ratio of offspring, exposed in utero or via the milk, were not affected by doses up to and including 500 mg/kg/day. The results observed in this screening study conclude that LZ649 has no effect on reproductive performance and offspring survival or development at doses up to and including 500 mg/kg/day."*

You have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2., weight of evidence. Hence, ECHA has evaluated your adaptation with respect to this adaptation.

To support your adaptation you have provided the following sources of information in IUCLID sections 7.5.1. and 7.8.1., respectively:

- Sub-chronic oral toxicity study with rats, OECD TG 408, GLP, reliability 1, with the

registered substance, and
- Screening study for reproductive/developmental toxicity, oral route, with rats, OECD TG 421, GLP, reliability 1, with the registered substance.

a) ECHA's evaluation and conclusion of the information provided

Evaluation approach/criteria

An adaptation pursuant to Annex XI, Section 1.2. requires sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property with respect to the information requirement in question including an adequate and reliable documentation while the information from each single source alone is regarded insufficient to support this notion.

Your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance with respect to a pre-natal developmental toxicity study (EU B.31/OECD TG 414). Relevant elements are in particular, exposure route, duration and levels, sensitivity and depth of investigations to detect pre-natal developmental toxicity (including growth, survival, external, skeletal and visceral alterations) and maternal toxicity. In particular relevance, reliability and consistency of results/data and coverage (completeness) need to be considered.

Evaluation of the provided information

While ECHA finds that the reliability and relevance of the studies specified above are adequate, the information you have provided is considered incomplete in regard of the standard information requirement, i.e. pre-natal developmental toxicity study, because the two studies provided. i.e. sub-chronic toxicity study and screening study for reproductive/developmental toxicity do not cover key parameters of a pre-natal developmental toxicity study, such as examinations of foetuses for skeletal and visceral alterations.

Hence, the sources of information you provided, together with your justification for the adaptation, do not allow to conclude on the dangerous (hazardous) property of the registered substance with respect to the information requirement for Annex IX, Section 8.7.2.

In your comments on the draft decsion you state that you agree with ECHA's evaluation and conclusion, that there is an information gap for this endpoint and the available data and justification are not complete to cover key parameters of a pre-natal developmental toxicity study.

Therefore, the general rules for adaptation laid down in Annex XI, Section 1.2. of the REACH Regulation are not met and your adaptation of the information requirement is rejected.

As explained above, 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.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

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 on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, 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.

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: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a first species (rat or rabbit) by the oral route.

Notes for your consideration

ECHA notes that a revised version of OECD TG 414 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. You should test in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

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.

The compliance check was initiated on 1 August 2017.

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 amended the request(s) by removing the following request: In vivo mammalian alkaline comet assay. A negative in vivo micronucleus (MN) test (OECD TG 474) assessed by ECHA under the follow up process (TPE-D-2114296279-32-01/F), is considered sufficient to fulfil this information requirement.

ECHA notified the draft decision to the competent authorities of the Member States for proposals 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 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, or to otherwise fulfil the information requirements with a valid and documented adaptation, 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.