EUROPEAN CHEMICALS AGENCY

Helsinki, 28 May 2019

Addressee: [redacted]

Decision number: CCH-D-2114470948-31-01/F
Substance name: 1,1'-DITHIOBIS[HEXAHYDRO-2H-AZEPIN-2-ONE]
EC number: 245-910-0
CAS number: 23847-08-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 19/09/2017
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. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats 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 **4 December 2020**. 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 **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. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

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.

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. 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.

In the technical dossier you have provided a study record for a "repeated dose 28-day oral toxicity study" (test method: OECD TG 407). However, this study does not provide the information required by Annex IX, Section 8.6.2., because exposure duration is less than 90 days, and the number of animals per dose group is significantly lower than in the 90 day sub-chronic toxicity study (OECD TG 408). Therefore, the sensitivity of a 28-day study is lower than that of a sub-chronic toxicity study.

You have also sought to adapt this information requirement. In your adaptation, you have referred to Annex XI, and the criteria given in Section 1.1.2 of the REACH Regulation. ECHA has assessed your adaptation as follow.

First, ECHA underlines that the provisions of Annex XI, Section 1.1.2. REACH foreseen that testing does not appear scientifically necessary when data from studies which are *not carried out according to GLP or the test methods referred to in Article 13(3)*" can be considered equivalent to data generated by the corresponding test method referred to in Article 13(3) REACH. Since the only study you refer to is made according to the OECD test guideline 407, and was made under GLP, your adaptation does not seem to fall within the scope of Annex XI, 1.1.2.

Nevertheless, ECHA has evaluated your arguments against the specific criteria of Annex XI, Section 1.1.2 REACH.

The first criterion you have addressed is the adequacy of the study *"for the purpose of classification and labelling and risk assessment*." In relation to that criteria, you claim that similar examinations (hematology, clinical chemistry etc.) are covered in a 28-day repeated dose toxicity study and in 90-day repeated dose toxicity study. You further claim that according to ECHA Guidance, time extrapolation is not necessary for local effects, and that in the 28-day study, there was no indication of systemic effects.

ECHA considers, however, that it cannot be excluded that other effects, in addition to those seen in the forestomach, may be observed in a 90-day study, because the exposure duration is longer. Since the LOAEL in the 28-day study is close the threshold for STOT RE in the CLP Regulation, it cannot be ruled out that with a more sensitive 90-day study, criteria of the STOT classification may be met. Therefore, it is concluded that the data provided is not adequate for classification.

You have provided comments on this criterion and argued that it is unlikely that severe effects, which would no longer be adaptive ones, would be seen in the sub-chronic toxicity study. After analysing your reasoning, ECHA is of the opinion that it is based on assumptions. For this substance, which shows toxic effects at a relatively low dose level, the sub-chronic study is necessary in order the characterise the properties according to the information requirement specific to this tonnage. Furthermore, ECHA is of the opinion that the current data is not conclusive for the purpose of classification and/or risk assessment, as required in the 1st criterion of the Annex XI, 1.1.2.

The second criterion of Annex XI, Section 1.1.2 refers to "*adequate and reliable coverage of key parameters foreseen to be investigated...*" You claim that all key parameters were investigated in the 28-day study. ECHA agrees that in terms of key parameters, the 28-day and 90-day studies do not differ remarkably. However, the duration of exposure in these two studies differs. You claim that "*due to the irritating properties of the test substance, prolonged exposure to irritating concentration at the point of entry, the forestomach will not lead to additional relevant information concerning the endpoint repeated dose toxicity*." This statement has not been demonstrated with relevant information, and furthermore, ECHA notes that by default, a 90-day study is a more sensitive study and effect not seen in a 28-day study may be observed in a 90-day study. Therefore, the coverage of the key parameters foreseen to be investigated by a 90 days study is not adequate in the study you submitted.

You have provided comment also on this criterion and argued that a sub-acute study is adequate, because the substance is not considered to accumulate over time to an extent showing relevant systemic effects. ECHA notes that you have not supported this consideration with relevant data. Furthermore, ECHA points out that in addition to accumulation of the substance, also accumulation of the effect(s) may take place, and/or the physiological reserve capacity may decrease. Therefore, a sub-chronic study may provide evidence of higher toxicity as compared to the sub-acute study.

The third criterion requires that the duration of the exposure in the available experimental study is comparable to the test method referred to in Article 13(3), i.e. sub-chronic toxicity study in this case. ECHA notes that the duration of a 28 day study is not comparable to a 90 day study, and therefore this criterion is not met.

In your comments on this criterion, you have pointed to some scientific articles that discuss the limited value of the sub-chronic study. Recognising that there are cases, where sub-chronic study does not provide additional information as compared to the results of the sub-acute study, ECHA considers that no adequate substance-specific information was provided, which shows that it would be the case for this substance. Furthermore, you suggest that increasing the duration of the study would most likely lead to additional structural alterations of the stomach, and not to any relevant effects associated with general systemic toxicity. ECHA is of the opinion that based on the current information, detection of signs of other general systemic toxicity in a sub-chronic study cannot be excluded.

The fourth criterion concerns adequate and reliable documentation. ECHA finds that the sub-acute toxicity study has been adequately documented, but because the four criteria of Annex XI, Section 1.1.2 are cumulative, and three other criteria are not met, this adaptation is not acceptable.

In your comment on the fourth criterion you refer to the OECD TG 414 study that provides further documentation. ECHA notes that the gestation period for rats varies from 21 to 24 days, which is similar to the maximum duration of the OECD 414, and that is even a shorter duration than in the sub-acute toxicity study. Therefore, OECD TG 414 study does not provide evidence that longer duration would not reveal any relevant new information.

Therefore, ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI; Section 1.1.2., 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.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 5.0, December 2016) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, according to the Chemical Safety Report, risk management measures are in place to prevent exposure of humans via inhalation. Hence, the test shall be performed by the oral route using the test method OECD TG 408.

According to the test method OECD TG 408 rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

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: Repeated dose 90-day oral toxicity study (test method: OECD TG 408) in rats.

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 March 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 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.