EUROPEAN CHEMICALS AGENCY

Helsinki, 27 July 2017

Addressee: [redacted]

Decision number: CCH-D-2114366663-42-01/F
Substance name: N,N-DIETHYLHYDROXYLAMINE
EC number: 223-055-4
CAS number: 3710-84-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 14/04/2016
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:

Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./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 **5 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

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 inhalation toxicity study" (test method: OECD TG 412). 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. Therefore, the sensitivity of a 28-day study is much lower than that of a 90-day study.

You have also provided a study record for a 2-year inhalation study in rats (publication from 1981). In this study, one group of test animals was exposed to the registered substance together with the vapor of diethylamine hydrogen sulfite, and another group of test animals was exposed to the registered substance together with the vapor of diethylamine hydrogen sulfite and nitroethane (10 ppm). The concentrations of the registered substance used in this experimental study were within the range of 9 – 27 ppm.

You have sought to adapt this information requirement according to Annex IX, Section 8.6.2., column 2. You provided the following justification for the adaptation:

"According to specific rules for adaptation from column 1 requirement, "the sub-chronic toxicity study (90-day) does not need to be conducted if: a reliable chronic toxicity study is available, provided that an appropriate species and route of administration were used". A reliable 28-day inhalation study (OECD TG # 412) together with a limited 2-year inhalation study in rats are available and considered as sufficient to assess the long-term effect of diethylhydroxylamine exposure. To perform a 90-day inhalation study would be not of any added value in term of hazard identification and risk assessment, considering the assessment factor used to derive a long-term DNEL from a sub-acute NOAEC."

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 8.7.2., column 2 for the following reasons:

(i) The repeated dose 28-day inhalation toxicity study available does not show severe effects according to the criteria for classifying the substance as STOT RE.

(ii) The 2-year inhalation study (chronic study) is not adequate and reliable for drawing conclusions for the purpose of classification and labelling and/or risk assessment as the doses used in the 2-year study were low when compared to the doses used in the 28-day inhalation study. In addition, the chronic study was performed with co-administration of other substances. Due to co-exposure of animals to other substances the toxicity of the registered substance cannot be assessed, i.e. it cannot be ruled out that e.g. synergistic/antagonistic interaction occurs. Thus, the study is not considered reliable to draw conclusions for the purpose of classification and labelling and/or risk assessment for sub-chronic exposure, either as standalone evidence or in combination with the 28-day repeated dose inhalation study.

(iii) There is no experimental evidence that the registered substance undergoes immediate disintegration.

(iv) There is experimental evidence that the substance is absorbed with evidence of toxicity in the 28-day inhalation study.

Due to reasons explained above ECHA considers that the long-term effects of the registered substance cannot be assessed based on the 28-day and 2-year studies available. Although, the long-term DNEL can be derived with extrapolation from the sub-acute study, the information available does not allow to conclude on the hazardous properties of the substance for classification purposes after repeated exposure.

Therefore, your adaptation of the information requirement is rejected. 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 6.0, June 2017) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, even though the information indicates that human exposure to the registered substance by the inhalation route is likely, potential inhalation-specific effects are already addressed by providing a sub-acute toxicity study by the inhalation route and by deriving a long-term DNEL for inhalation, local effects. In addition, ECHA identified that a 28-day oral repeated dose toxicity study with the registered substance is available in the public domain by the Japanese Chemicals Collaborative knowledge database (JCHEC) through eChemPortal (http://www.safe.nite.go.jp/jcheck//direct.action?TYPE=DPAGE1&CAS=3710-84-7&MITI=2-190). The findings reported in the 28-day oral study indicate that the oral route might be more relevant for conclusions regarding classification and labelling for repeated exposure and target organ toxicity. The effects observed in the oral study can be considered more severe when compared with the effects from the 28-day inhalation study. Therefore, there is a need to further investigate these effects in an oral sub-chronic study.

Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method EU B.26./OECD TG 408 the 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: EU B.26./OECD TG 408) in rats.

Deadline to submit the requested information in this decision

In the draft decision communicated to you, the time indicated to provide the requested information was 18 months from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of the timeline from 18 months to 24 months. You sought to justify this extension to the deadline request by the following reasons:
(a) Your intention to perform a two week preliminary range finding study in order to fine tune the dose-levels of the 90 days toxicity study.
(b) Your intention to add to the 90 days study design a treatment free recovery period of at least 6 weeks to observe whether the effects that would have been observed are reversible (a recovery period was also scheduled in the 28-day oral toxicity study).
(c) To cover any technical issues that may arise from the implementation of the analytical method or during the experimental phase.
(d) Limited capacity of the laboratory.
In addition, the argument on the limited capacity of the laboratory to perform the test within a set timeline was supported by adequate documentation from the laboratory that is going to perform the test that this is the case.
ECHA notes the deadline of 18 months includes time to undertake a preliminary range finding study and a treatment free recovery period. However, based on the registrant's comments on the draft decsion concerning limited capacity of the laboratory, ECHA has granted the request and set the deadline for providing the requested information to ECHA in a dossier update to 24 months from the date of adoption of the decision. Therefore, ECHA has modified the deadline of the decision from 18 months to 24 months.

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 21 Februaray 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 deadline. You agreed to perform the draft decision request.

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.