EUROPEAN CHEMICALS AGENCY

Helsinki, 26 April 2017

Addressee: [redacted]

Decision number: CCH-D-2114359259-38-01/F
Substance name: REACTION PRODUCT OF MALEIC ANHYDRIDE, 2-ETHYLHEXYLAMINE AND TRIETHANOLAMINE
EC number: 939-488-3
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 02.05.2013
Registered tonnage band: 100-1000T

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: EU B.26./OECD TG 408) in rats with the registered substance;**

2. **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 of the REACH Regulation. In order 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 an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **3 May 2019**. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. 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, shall 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.)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of 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 "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422).

In addition, you provided the following justification in the registration dossier: "*As shown in a Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test (OECD 422) in which female rats were even treated for up to 57 days, no substance-induced effects have been observed up to the limit dose. These data suggest that prolongation of treatment up to 90 days is unlikely to induce any adverse effects. Considering animal welfare, it is hence not justifiable to perform another study, which is unlikely to add any further information to the evaluation of the risk of the test substance to human health*".

ECHA notes that while you have not explicitly claimed an adaptation, your justification and the indicated supporting study (OECD TG 422) could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.1.2., use of existing data.

However, ECHA observes the following shortcomings in the study design of the provided OECD TG 422 compared to the required sub-chronic toxicity study (OECD TG 408):

- Histopathological examinations were performed only for 5 animals/sex/dose group instead of 10 animals/sex/dose as required according to OECD TG 408 apart from the sex organs (ovaries, oviducts, uterus, cervix, vagina, testes, epididymides, seminal vesicles, coagulation glands and prostate)
- While organ weights for uterus and ovaries were not provided, adrenals, brain, heart, kidneys, liver, spleen and thymus were only weighted for only 5 animals/sex/dose group instead of 10 animals/sex/dose as required according to OECD TG 408
- The provided supporting study (OECD TG 422) has a shorter exposure duration (28 days for male animals and 57 days for female animals) than a sub-chronic toxicity study according to OECD TG 408 (90 days)

You further assume that "*no substance-induced effects have been observed up to the limit dose. These data suggest that prolongation of treatment up to 90 days is unlikely to induce any adverse effects. Considering animal welfare, it is hence not justifiable to perform another study*". However, ECHA points out that significant increased relative liver weight (males) and kidney weights (both sexes) were reported at the highest dose of 1000 mg/kg bw/d. Hence, in a study with prolonged exposure duration of 90 days, the observed effects might become adverse and other adverse effects might occur which were not detected in the OECD TG 422 screening study.

Taking into account the above considerations, ECHA concludes that the specific criteria for adapting the information requirement of sub-chronic toxicity study pursuant to Annex XI, 1.1.2., use of existing data, are not met. 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 4.1, October 2015) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance is a liquid of very low vapour pressure. Uses with industrial and professional spray application are reported in the chemical safety report. However, the reported concentrations are low (< [redacted]%). 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.

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

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

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 not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2.
You have provided the following justification in the registration dossier to adapt the standard information requirement:

"*As shown in a Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test (OECD 422), no substance-induced effects have been observed for the reproduction organs in male and female rats treated up to the limit dose of 1000 mg/kg/d. Fertility and reproductive performance were also unaffected by treatment. Furthermore, pups of animals treated with the test item did neither exhibit any malformations nor showed alterations in body weight, sex ratio or organ development (macroscopically). Considering these data, it is unlikely that adverse effects will be detected in a further study. Due to animal welfare, it is therefore not justified to perform any further studies, which do most likely not add any further information to the evaluation of the toxicity of the test item.*"

ECHA notes that while you have not explicitly claimed an adaptation, your justification and the indicated supporting study (OECD TG 422) could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.1.2., use of existing data.

However, ECHA observes that the OECD TG 422 screening study does not provide the information required by Annex IX, Section 8.7.2., because it does not cover key parameters of a pre-natal developmental toxicity study like caesarean section of the pregnant animals and examinations of foetuses for skeletal and visceral alterations.

You further argue that "*pups of animals treated with the test item did neither exhibit any malformations nor showed alterations in body weight, sex ratio or organ development (macroscopically). Considering these data, it is unlikely that adverse effects will be detected in a further study.*" However, based on the lower statistical power of the OECD TG 422 screening study (10 pregnant animals per dose) compared to the pre-natal developmental toxicity study (20 pregnant animals per dose), and since the OECD TG 422 screening test is not a definitive test method to conclude on the absence of pre-natal toxic effects, your justification cannot be considered valid to adapt the standard information requirement for a pre-natal developmental toxicity study.

Taking into account the above considerations, ECHA concludes that the specific criteria for adapting the information requirement of a pre-natal developmental toxicity study pursuant to Annex XI 1.1.2., use of existing data, is not met. Therefore, 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 standard 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 4.1, October 2015) R.7a, chapter 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.

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 9 August 2016.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA did not receive any comments by the end of the commenting period.

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 request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In carrying out the test(s) required by the present decision it is important to ensure that the particular sample of substance tested 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. If the registration of the substance covers different grades, the sample used for the new test(s) must be suitable to assess these. Furthermore, there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.