Helsinki, 17 September 2019

Addressee: [redacted]

Decision number: CCH-D-2114482893-34-01/F
Substance name: Amines, C10-C14-tert-alkyl
EC number: 701-175-2
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 19/12/2018
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. ***In vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method: OECD TG 473) or *in vitro* micronucleus study (Annex VIII, Section 8.4.2., test method: OECD TG 487) with the registered substance;**

2. **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 have to submit the requested information in an updated registration dossier by **24 September 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 Wim De Coen, 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

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.

In rour registration dossier assessed for the initial draft decision based on submission number [redacted] with a submission date of 13/11/2017, ECHA considered it contained, for multiple endpoints, adaptation arguments in the form of a grouping and read-across approach under Annex XI, Section 1.5. of the REACH Regulation. ECHA considered you wanted to achieve compliance with the REACH information requirements for the registered substance Amines, C10-C14-tert-alkyl (EC number: 701-175-2) (hereafter the 'target substance') using data of a structurally similar substance amines, C12-C14 tert alkyl (EC no 273-279-1) (hereafter the 'source substance') for the following endpoints:

1. Partition coefficient n-octanol/water (Annex VII, Section 7.8.)
2. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
3. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
4. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
5. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)
6. Screening study for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
7. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

You updated your registration dossier with the submission number [redacted] with a submission date of 19/12/2018. ECHA accepted your updated dossier. In the relevant technical sections of the above endpoints, you indicate that the test material in the studies were preformed using PRIMENE 81-R Amine [redacted], which constitutes 100 % of "Amines, C10-C14-tert-alkyl Amines, C10-C14-tert-alkyl 701-175-2.", the registered substance. Therefore, ECHA concludes that for the above endpoints, there is no read-across adaptation present. As a result the read-across adaptation section in the initial draft decision has been removed.

- Partition coefficient n-octanol/water (Annex VII, Section 7.8.)
- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species,

As the above relevant valid tests have been made with the registered substance, the dossier is considered compliant for these endpoints, and the respective requests have been removed from the draft decision.

Regarding the screening study for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.), in your updated dossier and in your comments on the draft decision, you have provided an adaptation which states, "In accordance with column 2 of REACH Annex VIII a screening study for reproductive developmental toxicity does not need to be performed if a pre-natal developmental toxicity study is available. A prenatal development study (OECD TG 414) using the registered substance has been conducted as described in the dossier".
As the pre-natal developmental toxicity study on the registered is valid, your adapation is

acceptable. ECHA has removed this request from the draft decision.

Regarding, In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.) and the Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.), whilst you confimed that the relevant tests have been made with the registered substance, the studies are still not considered adequate and therefore, the respective information requests have not been removed from the present draft decision. Further information is in the respective endpoints, below.

1. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)

An "*In vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study" is a standard information requirement as laid down in Annex VIII, Section 8.4.2. 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.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for *in vivo* micronucleus study with the source substance, *amines, C12-C14 tert alkyl,* EC no 273-279-1. However, as explained above in Appendix 1, section 0 of this decision, your adaptation of the information requirement is rejected. As stated above, based on your comments and the updated dossier, there is no read-across adaptation present.

However, as stated in the inital draft decision, , the study submitted by you does not provide the information required by Annex VIII, Section 8.4.2, because you did not demonstrate that the bone marrow was exposed to the test substances, as required in the OECD Test Guidline 474 (paragraph 48), in case the conclusion is drawn that the test result is negative.

In your comments to the draft decision you outline your proposal to provide an adaptation for this information requirement. ECHA considers it is your responsibility if you wish to undertake additional testing and/ or analysis in order to support an adapatation for the current request. You propose to undertake some additional analysis to assess the bioavailability of the substance via the oral route of exposure which will be compared to the in silico prediction of systemic bioavailability using Gastroplus. ECHA cannot currently assess if your proposal for adapation would be acceptable, however, ECHA outlines that your proposed analysis is not comparable in duration to an *in vitro* cytogenicity study in mammalian cells or in vitro micronucleus study and it does not give the same information as these tests do. ECHA will evaluate your information after the deadline of this decision according to the specific rules of column 2 adaptations and adaptation(s) according to Annex XI.

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 considers that the *in vitro* mammalian chromosome aberration test (test method OECD TG 473) and the *in vitro* mammalian cell micronucleus test (OECD TG 487) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.2. of the REACH Regulation.

According to your comment and confirmed in the present dossier submission (No [redacted]), the test material in the respective study is referred to as PRIMENE 81-R Amine [redacted] which constitutes 100 % of "Amines, C10-C14-tert-alkyl Amines, C10-C14-tert-alkyl 701-175-2.", i.e. the registered substance. Therefore, ECHA concludes that for this endpoint, compliance of the dossier does not depend on the read-across.

However, regardless of the identity of the test substance, the study submitted you did not demonstrate that the bone marrow was exposed to the test substances, as required in the OECD Test Guidline 474 (paragraph 48).

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: *In vitro* mammalian chromosome aberration test (test method: OECD TG 473) or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487).

2. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

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 toxicity study, via inhalation" (test method: OECD TG 412) with the source substance. 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 413 or OECD TG 408). Therefore, the sensitivity of a 28-day study is much lower than that of a 90-day study.

In addition, you have provided a following adaptation: *"a sub-chronic toxicity study (90 days) does not need to be conducted because a reliable short-term toxicity study (28 days) is available showing severe toxicity effects according to the relevant criteria for classifying the substance, for which the observed NOAEL-28 days, with the application of an appropriate uncertainty factor, allows the extrapolation towards the NOAEL-90 days for the same route of exposure (In accordance with Annex XI section 2, the substance is corrosive in the dose range of interest for the study and for animal welfare reasons should be avoided.)"*

First, ECHA notes that there is adaptation possibility under REACH Annex IX, 8.6.2. column 2, according to which *"the sub-chronic toxicity study does not need to be conducted is a reliable short-term toxicity study is available showing severe toxicity effects according to the criteria for classifying the substance as R48 (corresponds H372/H373 under CLP, EC No 1272/2008), for which the observed NOAEL-28 days, with the application of an appropriate uncertainty factor, allows extrapolation towards the NOAEL-90 days for the same route of exposure."* However, since ECHA notes that you have not self-classified your substance according to this adaptation, ECHA cannot determine, whether you conclude that the relevant classification criteria are met.

Therefore, this adaptation of the information requirement is rejected.

Secondly, you have proposed to adapt the information in accordance with Annex XI section

2. You have justified the proposal for adaptation with a reference to corrosivity of the registered substance.

While Annex XI section 2 does not refer to corrosivity, according to the REACH Regulation "*in vivo* testing with corrosive substances at concentration/dose levels causing corrosivity shall be avoided" (Annex IX, fourth paragraph). However, ECHA would like to point out that non-corrosive concentration(s) can be tested. Therefore, this is not according to the specific rules indicated in Annex IX or Annex X section 2 for adapting standard information requirements. Recognising that the registered substance is classified as Skin Corr. 1B, you are advised to examine how the concentration and pH of the test substance in (buffered) vehicle can be adjusted to avoid corrosion, while allowing the detection of potential systemic toxicity effects of the substance. The general principle of adjusting the concentration of the test substance to avoid corrosion and irritation is set out in the relevant test guidelines (OECD TG 413 and OECD TG 408).

Therefore, this adaptations 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 6.0, July 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 possible, 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. Hence, the test shall be performed by the oral route using the test method OECD TG 408.

ECHA acknowledges that in your comment, you have agreed to perform the requested test. In addition, ECHA notes that you propose to undertake some additional analysis to assess the bioavailability of the substance via the oral route of exposure which will be compared to the in silico prediction of systemic bioavailability using Gastroplus in order to provide futher support for your adapation. ECHA has addressed your comment under request 1 above.

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

ECHA took into account your comments and your updated dossier and amended the request(s) and the deadline. As outlined above, as a result of no read-across adaptation the following requests have been removed: Partition coefficient n-octanol/water; In vitro gene mutation study in bacteria; In vitro gene mutation study in mammalian cells; Pre-natal developmental toxicity study in a first species.

Also, as the pre-natal developmental toxicity study on the registered is valid, the adapation for the screening study for reproductive/developmental toxicity is acceptable. ECHA has removed this request from the draft decision.

Following a re-assessment of the accepted updated dossier, the scientific reasoning in the initial draft decision, ECHA will need to re-examine the scientific reasoning for the environmental fate and behaviour and aquatic endpoints. In light of this, ECHA has removed the following environmental fate and behaviour and aquatic requests from this draft decision: Long-term toxicity testing on aquatic invertebrates; Simulation testing on ultimate degradation in surface water; Identification of degradation products; Bioaccumulation in aquatic species.

As a result of the removal of these draft decision requests, ECHA has amended the draft decision deadline from 24 months to 12 months.

The compliance check was initiated on 01 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 within 30 days of the notification.

ECHA took into account your comments, your updated dossier and amended the request(s) and deadline.

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.