EUROPEAN CHEMICALS AGENCY

Helsinki, 5 April 2017

Addressee: [redacted]

Decision number: CCH-D-2114356498-35-01/F
Substance name: 3-aminomethyl-3,5,5-trimethylcyclohexanamine
EC number: 220-666-8
CAS number: 2855-13-2
Registration number: [redacted]
Submission number: [redacted]
Submission date: 26.01.2015
Registered tonnage band: 1000+T

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 X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rabbit), oral route with the registered substance;**

2. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce some toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;**

3. **Identification of degradation products (Annex IX, 9.2.3.).**

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 **13 April 2020**. 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

TOXICOLOGICAL INFORMATION

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to X of 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 X, Section 8.7.2.) in a second species

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

The technical dossier contains information on a pre-natal developmental toxicity study in rats by the oral route using the registered substance as test material.

However, there is no information provided for a pre-natal developmental toxicity study in a second species. Furthermore, the technical dossier does not contain an adaptation in accordance with column 2 of Annex X, Section 8.7.2. or with the general rules of Annex XI for this standard information requirement.

In your comments on the draft decision according to Article 50(1) of the REACH Regulation you have commented that "*based on the outcome of the developmental toxicity test and all other relevant available data there is no need to perform a study on a second species*".

ECHA notes that you propose an adaptation referring to Annex X, Section 8.7.2. read in conjunction with Annex IX, Section 8.7.2., column 2, which requires that "*a decision on the need to perform a study at this tonnage level or the next on a second species should be based on the outcome of the first test and all other relevant available data*." However, for Annex X dossiers a pre-natal developmental toxicity study in a second species is a standard information requirement. The prenatal developmental toxicity study in a second species can be omitted, if, taking into account the outcome of the first test and all other relevant available data, an adaptation pursuant to REACH Annex X, Section 8.7, Column 2 or pursuant to REACH Annex XI can be justified (see ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015), Chapter R.7a, section R.7.6.2.3.2, Stage 4.5).

You have provided several arguments to adapt the information requirement which you summarise as follows: "*The toxicological information regarding effects on Developmental toxicity (CIT, 2002; see section 7.8.2 of IUCLID) and the fact that IPDA do not cause adverse effects on the examined reproductive organs in the 90 day subchronic study (RCC, 1986; see section 7.5.1 of IUCLID) leading to the conclusion that effects on fertility of the substance at doses, which do not cause parental toxicity, are rather unlikely. All taken together, including the physicochemical properties of IPDA, further studies will not bring more information and are therefore not necessary.*" In addition, you indicated that you will provide these arguments with an update of the dossier.

ECHA notes that the arguments presented in the comments neither meet the specific rules of Annex X, Section 8.7, column 2 nor the general rules of Annex XI of the REACH Regulation.

ECHA also notes one of your argument stating that "*Rabbits are known to be more sensitive than rats against corrosive substances. In case of testing with rabbits, the testing doses has to be reduced so far that systemic effects also will not expected.*" It has to be noted that test method OECD TG 414 and ECHA *Guidance on information requirements and chemical safety assessment* (version 4.1, October 2015), Chapter R.7a, section R.7.6.2.3.2, Stage 4.5 indicate that the rat and the rabbit are the preferred species. However, ECHA Guidance further indicates that "*The selection of the species for the prenatal developmental toxicity study should be made taking into account substance-specific aspects. If a species other than the rat and the rabbit is selected as the first or second species, the selection should be justified.*" Hence, the argument that rabbit might not be an appropriate species for testing cannot be accepted as an argument to adapt this information requirement for a second species.

ECHA notes further that the information mentioned in the comment has not been provided yet in the Registration Dossier. Hence, the compliance of this information will be examined by ECHA in your updated registration after the deadline set in the adopted decision has passed.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not currently meet the information requirement. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

The test in the first species was carried out with rats. According to the test method EU B.31./OECD 414, the rabbit and the rat are the preferred species. On the basis of this default assumption, ECHA considers that the test should be performed preferably with rabbit as a second species. However, if based on the available information and/or substance-specific properties the results from the rabbit would not be appropriate for human health hazard and risk assessment, you should - based on a scientific justification - use another mammalian laboratory animal as second species which is appropriate and relevant for human health hazard assessment and therefore commonly used in pre-natal developmental toxicity testing.

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 second species (rabbit) by the oral route.

2. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

a) The information provided

You have not provided any study record of an extended one-generation reproductive toxicity study in the dossier that would meet the information requirement of Annex X, Section 8.7.3.

You have sought to adapt this information requirement [according to Annex X, introductory paragraph 5 and Annex XI, Section 1.2.]. You provided the following justification for the adaptation:

"According to section 1.2 of Annex XI, the study need not be done if there is a weight of evidence to conclude the substance does not have a particular property, and further testing on vertebrate animals may be omitted. Furthermore Annex X states: "When, for certain endpoints, it is proposed not to provide information for other reasons than those mentioned in column 2 of this Annex or in Annex XI, this fact and the reasons shall also be clearly stated. "

Justification for waiving: The toxicological information regarding effects on Developmental toxicity (no abortation or total resorption, no treatment releated effects on the pre- or post-implantation loss, no treatment releated effects on sex-ratio and on the fetal weight; CIT, 2002; see section 7.8.3 of IUCLID5) and the fact that Isophorone diamine does not cause adverse effects on the examined reproductive organs in a 90 day subchronic study (no effects on epididymides, mammary gland, ovaries, seminal vesicles, testes and uterus in concentrations up to 160 mg/kg bw/day, Testes weights were also not affected; RCC, 1986; see section 7.5 of IUCLID) leading to the conclusion that that effects on fertility of the substance Isophorone diamine at doses, which do not cause parental toxicity, are rather unlikely. Therefore further studies regarding effects on fertility are not necessary for Isophorone diamine."

To support your weight of evidence approach, you have provided the following study summaries:

- Sub-chronic oral toxicity study according to OECD TG 408 (RCC 1986) (IUCID section 7.5.1);
- A pre-natal developmental toxicity study in rats according to OECD TG 414 (CIT 2002) (IUCLID section 7.8.2).

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

Criteria applied

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 (hazardous) property with respect to the information requirement in question including an adequate and reliable documentation.

To appropriately address the information requirement in question, your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance at equivalent confidence level as investigated in an extended one-generation reproductive toxicity study (EU B.56./OECD TG 443) as requested in this decision. ECHA considers that this study type provides relevant information on two aspects, namely on sexual function and fertility in P and F1 generations (further referred to as "sexual function and fertility") and on developmental toxicity observable peri- and postnatally in the F1 generation (further referred to as "post-natal developmental toxicity").

Relevant elements for sexual function and fertility are in particular functional fertility (mating behaviour, conception, pregnancy, parturition, and lactation) in the parental generation after 10 weeks pre-mating exposure and histopathological examinations of reproductive organs in parental generation.

Relevant elements for post-natal developmental toxicity are in particular peri- and post-natal investigations of the F1 generation up to adulthood (such as growth, survival/mortality, external malformations and sexual maturation).

Sexual function and fertility

With respect to the aspect of sexual function and fertility of P and F1 generation, you have provided reliable information on histopathological changes in major reproductive organs (90 day sub-chronic toxicity study OECD TG 408). However, ECHA notes that investigations regarding sexual function and fertility are not included.

Thus, the information you provided does not support your conclusion that the substance does not have a dangerous property with respect to sexual function and fertility.

Post-natal developmental toxicity

ECHA notes that your adaptation justification does not address the post-natal develop-mental toxicity. The provided information does also not cover the key elements which need to be investigated in this regard. The studies according to OECD TG 414 in the rat provide information only on pre-natal developmental toxicity.

These data do not cover the peri-and postnatal developmental toxicity. Thus, the information you provided does not support the conclusion that the substance does not have a hazardous property with respect to postnatal developmental toxicity.

In your comments on the draft decision according to Article 50(1) of the REACH Regulation you indicated that a dose range-finding study according to OECD TG 422 will be performed and that you will decide on the necessity of performing the requested extended one-generation reproductive toxicity study after the results of the range-finding study are available.

ECHA acknowledges the information provided in the comments. However, ECHA reminds you that a test according to EU B.56./OECD TG 443 is a standard information requirement and that in case you want to deviate from this you need to justify an adaptation according to column 2 of Annex X, Section 8.7. or Annex XI of REACH. Any adaptation has to be adequate and in line with the ECHA Guidance.

ECHA further notes that the information mentioned in the comment has not been provided yet. Hence, the compliance of this information will be examined by ECHA in your updated registration after the deadline set in the adopted decision has passed.

Conclusion

Hence, the information you provided to support you adaptation, considered individually or together, do not allow to assume/conclude that the substance does not have a particular dangerous (hazardous) property with respect to the information requirement for Annex X, Section 8.7.3.

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.

Consequently there is an information gap and it is necessary to provide information for this endpoint. Thus, an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. is required. The following refers to the specifications of this required study.

c) The specifications for the study design

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015), the starting point for deciding on the length of the premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015).

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Species and route selection

According to the test method EU B.56./ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats.

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.

d) Outcome

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: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. You may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the new information shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 4.1, October 2015). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

ECOTOXICOLOGICAL INFORMATION

3. Identification of degradation products (Annex IX, 9.2.3.)

The identification of the degradation products is a standard information requirement according to column 1, Section 9.2.3. of Annex IX 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.

Column 2 of Section 9.2. of Annex IX of the REACH Regulation specifies that further biotic degradation testing needs to be proposed if the chemical safety assessment according to Annex I of the REACH Regulation indicates the need to investigate further the degradation of the substance and its degradation products and that the choice of the appropriate test(s), which may include simulation degradation tests in appropriate media, depends of the results of the chemical safety assessment.

Column 2 of Section 9.2.3. of Annex IX of the REACH Regulation states that the identification of degradation products does not need to be provided if the substance is readily biodegradable.

ECHA notes that you have not provided information on the potential degradation products of the registered substance. However, ECHA notes that:

- The substance is not readily biodegradable. Only 8% removal of dissolved organic carbon (DOC) was observed after 28 days in a DOC Die-away test and 42.0% removal of DOC was observed after 31 days in an Aerobic Sewage Treatment, Activated Sludge Units test (OECD TG 303A). From neither of those two results can it be concluded that the substance was readily biodegradable. Furthermore in both tests DOC removal was measured, from which a distinction between actual biodegradation and adsorption is not possible.

- Pursuant to Annex XIII of the REACH Regulation "*the identification* [of PBT and vPvB substances] *shall also take account of the PBT/vPvB-properties of relevant constituents of a substance and relevant transformation and/or degradation products*". ECHA Guidance on information requirements and chemical safety assessment (version 2.0, November 2014), Chapter R.11.4.1. further specifies that "*constituents, impurities and additives are relevant for the PBT/vPvB assessment when they are present in concentration of ≥ 0.1% (w/w). This limit of 0.1% (w/w) is set based on a well-established practice rooted in a principle recognised in European Union legislation*. [...] *Similar arguments apply to relevant transformation/degradation products. The PBT/vPvB assessment should normally be carried out for each relevant transformation or degradation product*".

  ECHA notes that your chemical safety assessment does not contain any information on the degradation products and on whether they could be PBT/vPvB or not.

- Information on degradation products shall also be taken into account for the exposure assessment (Annex I 5.2.4. of the REACH Regulation) and for the hazard assessment (e.g. column 2 of Annex X 9.4 and Annex X 9.5.1 of the REACH Regulation). Finally, information on degradation products is required for the preparation of Section 12 of the safety datasheet (Annex II of the REACH Regulation).

As explained above, your dossier does not meet the information requirements for this endpoint. Consequently there is an information gap and it is necessary to provide information for this endpoint.

Aerobic mineralisation in surface water – simulation biodegradation (test method EU C.25. / OECD TG 309) is an appropriate test to obtain information on the primary degradation and the formation of major transformation products for substances that are not highly insoluble in water. Based on the information provided in your registration dossier, ECHA notes that your substance is completely miscible with water and is therefore in the applicability domain of the requested test. The analytical methods to be applied will have to be substance-specific in order to identify the transformation products. When analytically possible, the identification, stability, behaviour and molar quantity of those transformation products relative to the parent compound shall be evaluated. In addition, degradation half-life, log K_{ow} and potential toxicity of the transformation products may be investigated. As specified in the OECD 309 test guideline, higher concentrations of the test substance (e.g., >100 µg/L) could be used for the identification and quantification of major transformation products to overcome potential analytical limitations.

In your comments to the draft decision you indicated your intention to adapt the information requirement and provided a detailed justification for this adaptation. You have predicted the identity of the degradation products using model CATALOGIC 301C v09.13 (OASIS Catalogic V5.11.19). This model identified 112 metabolites. The biodegradability and log Kow of each of these metabolites were also estimated by the model. The vast majority of the metabolites present in concentration ≥ 0.1% were predicted to be not readily biodegradable and therefore potentially persistent or even very persistent. However, the log Kow values for all of the predicted metabolites were estimated to be less than 4.5 and therefore none of those metabolites is expected to have a high potential for bioaccumulation. You have concluded that neither the registered substance nor any of its degradation products present in concentration ≥ 0.1% were likely to be PBT/vPvB. ECHA-S agrees with this conclusion.

ECHA notes that the information mentioned in your comments needs to be included in the registration dossier itself.

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: Identification of the degradation products (Annex IX, Section 9.2.3.).

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 30 months from the date of adoption of the decision. In your comments on the draft decision according to Article 50(1) of the REACH Regulation you requested an extension of the deadline for submitting the requested information to 36 months.

You sought to justify this request with different reasons. ECHA acknowledges that more time might be required to perform dose-range finding studies before a pre-natal developmental toxicity study in rabbit can be conducted. Therefore, ECHA has granted the request and set the deadline to 36 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 19 October 2016.

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 requests but extended the 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 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 relation to the information required by the present decision, the sample of the substance used for the new test(s) 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 test(s) 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 test(s) must be suitable to assess these grades. Finally 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.