EUROPEAN CHEMICALS AGENCY

Helsinki, 25 April 2017

Addressee: [redacted]

Decision number: CCH-D-2114359787-29-01/F
Substance name: 1H-IMIDAZOLE-1-PROPYLAMINE
EC number: 225-730-9
CAS number: 5036-48-6
Registration number: [redacted]
Submission number: [redacted]
Submission date: 05.11.2014
Registered tonnage band: [redacted]

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. **Composition (Annex VI, Section 2.3.) of the registered substance;**
   - **Degree of purity**
   - **Concentration values**

2. **Description of the analytical methods (Annex VI, Section 2.3.7);**
   - **Identification and quantification of the impurities**

3. **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;**

4. **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 (pure composition);**

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 **2 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 Ofelia Bercaru, Head of Unit, Evaluation E3

[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. Composition of the substance (Annex VI, Section 2.3.)

Pursuant to Article 10(a)(ii) of the REACH Regulation, the technical dossier shall contain information on the identity of the substance as specified in Annex VI, Section 2 of the REACH Regulation. In accordance with Annex VI, Section 2 the information provided shall be sufficient to enable the identification of the registered substance.

According to chapter 4.2 of the "Guidance for identification and naming of substances under REACH and CLP" (Version 1.4, June 2016) hereafter referred to as the "SID Guidance", the following applies for well-defined substances:

- Each main constituent (i.e. the constituent present at ≥80% for mono-constituent substance or each constituent present at ≥10% and 80% for multi-constituent substance) shall be identified and reported individually; and
- Each impurity present at ≥1% or relevant for the classification and/or PBT assessment of the registered substance shall be identified and reported individually.
- For each constituent, the typical, minimum and maximum concentration levels shall be specified regardless of the substance type.

As a general rule, the compositional information should be completed up to 100%.

You reported in IUCLID section 1.2 for the composition "[redacted]" the degree of purity of >[redacted]%(w/w). However, the concentration range of the main constituent [redacted] was >[redacted]%(w/w). Calculating from the minimum degree of purity of [redacted]%(w/w), and the total of the maximum concentrations of the impurities ([redacted]%(w/w)), there remains potentially [redacted]%(w/w) of the composition unaccounted for.

Therefore, the composition is potentially not fully accounted for when compared to what is required to be reported for mono-constituent substances.

In your comments to the draft decision you agreed to the completion of the information requested, concerning the composition of the substance.

You are requested to revise for the composition "[redacted]" the degree of purity and the compositional information regarding the main constituent and the impurities, such that the composition is fully accounted for.

The information shall be included in section 1.2 of the registration dossier. Further technical details on how to report the compositon of a substance in IUCLID are available in the ECHA manual "How to prepare registration and PPORD dossiers" (https://echa.europa.eu/manuals).

2. Description of the analytical methods (Annex VI, Section 2.3.7.)

Pursuant to Article 10(a)(ii) of the REACH Regulation, the technical dossier shall contain information on the identity of the substance as specified in Annex VI, Section 2 of the REACH Regulation. In accordance with Annex VI, Section 2 the information provided shall be sufficient to enable the identification of the registered substance.

According to Annex VI, section 2.3.7 of the REACH Regulation, the registration needs to contain a "*Description of the analytical methods or the appropriate bibliographical references for the identification of the substance and, where appropriate, for the identification of impurities and additives. This information shall be sufficient to allow the methods to be reproduced*". This includes a description of the analytical methods, and the corresponding results, used in the identification and quantification of the main constituents and impurities required to be reported in the composition of the registered substance.

For the composition "[redacted]" included in IUCLID section 1.2, you have reported ammonium hydroxide as an impurity with typical concentration of <[redacted]%(w/w) and range [redacted]%(w/w). This impurity has been indicated to be relevant for the classification and labelling of the substance. The analytical report attached in section 1.4 "[redacted]" for this composition includes the result "[redacted]", however, you have not provided the description of the method used to analyse the ammonium hydroxide impurity.

Because of the missing description, the presence and quantification of ammonium hydroxide, as reported in IUCLID section 1.2, cannot be verified.

In your comments to the draft decision you agreed to complete the description of the analytical methods used.

Therefore, you are requested to provide a detailed description of the analytical method(s) used for identification and quantification of the impurity ammonium hydroxide. The description shall be sufficient for the method(s) to be reproduced and shall therefore include details of the experimental protocol followed, any calculation made and the results obtained.

In addition, you shall ensure that the composition reported in IUCLID section 1.2 is in line with the information provided in section 1.4, which shall be sufficient to identify and quantify the substance.

The information shall be included in section 1.4 of the registration dossier.

Further technical details on how to report the analytical information in IUCLID are available in the ECHA manual "How to prepare registration and PPORD dossiers" (https://echa.europa.eu/manuals).

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

Pursuant to Articles 10(a) (vii) and 12(1) of the REACH Regulation, a technical dossier registered at [redacted] 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 "repeated dose 28-day oral toxicity study" (test method: OECD TG 407, 1999, report number 38S0387/98052) conducted with the registered substance (pure composition). However, this study does not provide the information required by Annex IX, Section 8.6.2., because the 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.

In addition, you have sought to adapt 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 1.1 (testing does not appear scientifically necessary/use of existing data). You provided the following justification for the adaptation: "*Due to animal welfare and as there is no exposure to the general population, a 90-d study is not justified, because there were no indications for severe effects in the oral 28-d study ([redacted], 1999). The slight reduction of total protein and albumin receiving 1000 mg/kg bw was transient and statistically significant only in males. It is assumed that a further 90d study would not provide further relevant information with regard to the risk assessment. The uncertainty regarding the effect levels after chronic exposure is covered by the assessment factor of 6, which is considered to be a conservative approach as there is no indication for a specific organ toxicity or accumulation of the substance over time.*"

ECHA notes that this adaptation relies on the results of the study conducted according to OECD 407 (see above), which is assessed by ECHA as not providing the information required by Annex IX, Section 8.6.2. The facts that there were no severe effects observed in this study and that there is no exposure to the general population are not listed among the adaptation provisions in Annex XI, Section 1.1. Furthermore, a 90-day study is a standard information requirement at the Annex IX tonnage level and further justification for the need to cover this requirement with compliant information is not needed. Your final sentence of the justification appears to refer to the DNEL derivation. ECHA notes that the footnote to Annex XI, Section 3.2 (a) (ii) clearly states that a DNEL derived from a 28-day repeated dose toxicity study shall not be considered appropriate to omit a 90-day repeated dose toxicity study.

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 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 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 /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.

In your comments to the draft decision you agreed to perform a repeated dose 90-day oral toxicity study (EU B.26./OECD TG 408) in rats.

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.

4. 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 [redacted] 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.

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 421, 2012, report no. 80R0387/98R002) conducted with the registered substance (pure composition). However, this 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 examinations of foetuses for skeletal and visceral alterations.

In addition, you have sought to adapt 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 1.1. (testing does not appear scientifically necessary/use of existing data). You provided the following justification for the adaptation: *"Due to animal welfare reasons and as there is no exposure to the general population, a Prenatal Developmental Toxicity study (OECD414) is not justified, as there were no adverse findings up to the limit dose of 1000 mg/kg bw/d in the offspring of a Reproduction / Developmental Toxicity Screening Test (OECD421, [redacted] 2012)."*

ECHA notes that this adaptation relies on the results of the study conducted according to OECD 421 (see above), which is assessed by ECHA as not providing the information required by Annex IX, Section 8.7.2. ECHA notes that in contrast to the statement in your adaptation justification quoted above ("no adverse findings") there were a statistically significant reduction of the live birth index in the high dose group and a statistically significant increase of numbers of stillborn pups in the high dose group. This is attributed by you mainly to one female and is considered as in the range of normal variations, however further data are not provided to support this interpretation. ECHA considers that a concern remains, in particular since imidazole as a structurally related substance is classified as reproductive toxic substance Repr 1B and is present in the pure composition at a concentration between [redacted] % (w/w).

You did not provide mechanistic information which clarifies the potential role of the imidazole moiety in the registered substance with regard to potential pre-natal developmental effects. In any case, the claimed absence of adverse findings (if considered as a valid observation) in this study and no exposure to the general population are not listed among the adaptation provisions in Annex XI, Section 1.1. Furthermore, a pre-natal developmental toxicity study in a first species is `a standard information requirement at Annex IX tonnage level and further justification for the need to cover this requirement with compliant information is not needed.

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 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.

Composition to be tested

ECHA notes that in the registration dossier subject to this decision two compositions ([redacted]) are included with different concentrations of imidazole (CAS 288-32-4) as impurity. Imidazole has a harmonised classification as Repr category 1B, H360. The [redacted] composition contains a typical concentration of [redacted] % and up to [redacted] % (w/w) imidazole and is classified as Repr category 1B (H360) according to Article 11(1) and Annex 1, Section 3.7.3 of the CLP Regulation. The [redacted] composition contains imidazole at a typical concentration between [redacted] % (w/w) according to section 1.2 of the IUCLID file and is not classified for reproductive toxicity.

ECHA
EUROPEAN CHEMICALS AGENCY

According to REACH Annex IX, Section 8.7., Column 2, a pre-natal reproductive toxicity study does not need to be conducted, if the substance is known to cause developmental toxicity, meeting the criteria for classification as toxic to reproduction category 1A or 1B. This adaptation possibility of REACH also requires that the available data are adequate to support a robust risk assessment. On this basis ECHA considers, that testing of the [redacted] composition is not needed and testing of the [redacted] composition is requested.

In your comments to the draft decision you agreed to perform an oral pre-natal developmental toxicity study (EU B.31./OECD TG414) in a first species (rat or rabbit).

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 (pure composition) 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 15 November 2016.

ECHA notified you of the draft decision and invited you to provide comments.

In your comments you agreed to the draft decision. ECHA took your comments into account 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 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.