Decision Number: TPE-D-0000002663-74-04/F Helsinki, 20 December 2012

DECISION ON A TESTING PROPOSAL SET OUT IN A REGISTRATION PURSUANT TO ARTICLE 40(3) OF REGULATION (EC) NO 1907/2006

For Dicyclohexylamine, CAS No 101-83-7 (EC No 202-980-7), registration number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 40(1) of the REACH Regulation, ECHA has examined testing proposals set out in the registration dossier for dicyclohexylamine, CAS No 101-83-7 (EC No 202-980-7), submitted by [redacted] (Registrant), submission number [redacted], for 100-1000 tonnes per year.

In accordance with Articles 10(a)(ix) and 12(1)(d) of the REACH Regulation, the Registrant submitted the following testing proposals as part of the registration dossier to fulfil the information requirements set out in Annex IX:

- Annex IX, 8.4. *In vivo* mammalian bone-marrow chromosome aberration study;
- Annex IX, 8.6.2. Repeated dose toxicity, sub-chronic toxicity study: oral route;
- Annex IX, 8.7.3. Two-generation reproductive toxicity study: oral route; and
- Annex IX, 8.7.2. Pre-natal developmental toxicity study: oral route.

The present decision relates solely to the examination of the testing proposal for an *in vivo* mammalian bone-marrow chromosome aberration study, a sub-chronic toxicity study by the oral route (90-day), and pre-natal developmental toxicity study. The testing proposal for the two-generation reproductive toxicity study is addressed in a separate decision although all testing proposals were initially addressed together in the same draft decision.

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band of 100 to 1000 tonnes per year. This decision does not take into account any updates after 19 July 2012, the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) of the REACH Regulation.

This decision does not imply that the information provided by the Registrant in his registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the present dossier at a later stage.

The examination of the testing proposals was initiated on 18 October 2010.

ECHA opened a third party consultation for the testing proposals including testing on

vertebrate animals that was held from 15 March 2011 until 29 April 2011. ECHA received comments from third parties (see section III).

On 26 September 2011 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision. That draft decision was based on the submission number MF905391-47.

On 25 October 2011 ECHA received comments from the Registrant not fully agreeing to ECHA's draft decision.

On 26 January 2012 (submission number: RU292493-93) and on 16 March 2012 (submission number MU303734-17) ECHA received a dossier update including updated Chemical Safety Report.

ECHA considered the Registrant's comments and dossier updates received. On basis of the comments, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

On 19 July 2012 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals to amend the draft decision within 30 days of the receipt of the notification.

Subsequently, Competent Authorities of the Member States submitted proposals for amendment to the draft decision.

On 22 August 2012 ECHA notified the Registrant of proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on those proposals for amendment within 30 days of the receipt of the notification.

ECHA reviewed the proposals for amendment received and decided to amend the draft decision.

On 3 September 2012 ECHA referred the draft decision to the Member State Committee.

On 13 September 2012 the Registrant provided comments on the proposed amendments. The Member State Committee took the comments of the Registrant into account.

The draft decision was split into two draft decision documents: one relating to the testing proposal for a two-generation reproductive toxicity study and one relating to the testing proposals for an *in vivo* mammalian bone-marrow chromosome aberration study, a sub-chronic toxicity study by the oral route (90-day), and a pre-natal developmental toxicity study.

After discussion in the Member State Committee meeting on 23-24 October 2012, a unanimous agreement of the Member State Committee on the draft decision (relating to the testing proposals an *in vivo* mammalian bone-marrow chromosome aberration study, a sub-chronic toxicity study by the oral route (90-day), and pre-natal developmental toxicity study) as modified at the meeting was reached on 24 October 2012. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Testing required

Pursuant to Article 40(3)(d) of the REACH Regulation the originally proposed tests, namely EU method B.11 (*In vivo* mammalian bone-marrow chromosome aberration tests) for

provision of Annex IX, 8.4 is rejected. Instead the Registrant shall carry out in accordance with Article 40(3)(c) the following additional test in order to meet the requirements set out in Annex IX, 8.4 using the indicated test method:

- Mammalian spermatogonial chromosome aberration test (Annex IX, 8.4., EU method B.23.) in rat by the oral route;

Pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant shall carry out the following tests using the indicated test method and under the conditions set out further below:

- Oral subchronic toxicity study (90-day) (Annex IX, 8.6.2., EU method B.26.) in rat.
- Pre-natal developmental toxicity study (Annex IX, 8.7.2., EU method B.31.) in rat by the oral route.

The Registrant shall determine the appropriate order of the studies taking into account the possible outcome and considering the possibilities for adaptations of the standard information requirements according to column 1 or 2 provisions of the relevant Annexes of the REACH Regulation.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **20 December 2014** an update of the registration dossier containing the information required by this decision.

At any time, the Registrant shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other registrants.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposal of the Registrant for the registered substance and scientific information submitted by third parties.

a) Examination of the testing proposals

1. Mammalian spermatogonial chromosome aberration test

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation a testing proposal may be rejected and one or more additional tests may be imposed to fulfil the REACH information requirements intended to be covered by that testing proposal.

According to Section 8.4 of Annex IX of the REACH Regulation, if there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII and there are no results available from an *in vivo* study already, an appropriate *in vivo* somatic cell genotoxicity study shall be proposed by the Registrant. In addition, if there is a positive result from an *in vivo* somatic cell study available, the potential for germ cell mutagenicity study should be considered on the basis of available data, including toxicokinetic evidence. If no clear conclusion about germ cell mutagenicity can be made, additional investigations shall be considered.

For this substance there was a positive result in an *in vitro* chromosome aberration study, and therefore, *in vivo* chromosome aberration study is needed. However, the dossier already contains three *in vivo* mammalian erythrocyte micronucleus studies using the registered substance. Of these three, two studies in rat were clearly positive.

The micronucleus study in mouse was negative. Therefore, no more *in vivo* somatic cell genotoxicity studies are needed. Consequently, the testing proposal for *in vivo* somatic cell chromosome aberration study must be rejected. However, the two positive *in vivo* mammalian erythrocyte micronucleus studies trigger a need for a germ cell mutagenicity study. Since there is no clear evidence whether or not the substance reaches the germ cells, a mammalian spermatogonial chromosome aberration test is required.

ECHA received third party information concerning the testing proposal during the public consultation. For the reasons explained below (see section III b. Consideration of the information received during third party consultation) the information provided by third parties is not sufficient to fulfil this information requirement.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is required to carry out following studies to fulfil the endpoint requirement: Mammalian spermatogonial chromosome aberration test (Annex IX, 8.4., EU method B.23.) in rat by the oral route using the registered substance (dicyclohexylamine), whereas the originally proposed test, EU Method B.11 is rejected in accordance with Article 40 (3) (d).

2. Oral subchronic toxicity study (90-day)

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. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The most appropriate route of administration should be chosen, having regard to the likely route of human exposure. For dicyclohexylamine, the inhalation and dermal routes are relevant for workers. According to Column *2 of* section 8.6.2 of Annex IX, the inhalation route is regarded appropriate if exposure via inhalation is likely taking into account the vapour pressure of the substance and/or the possibility of exposure to aerosols, particles or droplets of inhalable size.

The Registrant proposed testing by the oral route. ECHA noted in the draft decision that the substance has a low vapour pressure (7.5 Pa in 25° C). There is no information of size of droplets or aerosol particles. However, in the exposure assessment, inhalation exposure varies between 0.08 mg/m^3 and 0.23 mg/m^3 in different exposure scenarios. The substance is corrosive to skin and therefore is expected to act also as a respiratory tract irritant. Since no valid inhalation studies are available, a long-term worker DNEL for local effects in the respiratory tract could not be derived and no risk characterisation regarding the corrosive/irritating effects of the substance on the respiratory tract is possible. The risk characterisations ratios for the inhalation route vary between 0.05 and 0.64 for systemic effects. These risk characterisation ratios can not be applied for local effects at the respiratory tract, since there were no local respiratory DNEL. Testing by dermal route is not appropriate, since skin contact is not likely due to skin corrosivity of the substance.

Therefore, testing for repeated dose toxicity (90 day) by the inhalation route was regarded more appropriate than by the oral route. Consequently, in the initial draft decision the testing proposal for subchronic toxicity study (90-day) by the oral route was rejected and the Registrant was required to carry out instead a subchronic toxicity study (90-day) by the inhalation route.

The Registrant, in his comments submitted according to Article 51(1) of the REACH

Regulation, provides measured data on inhalation exposure. The measured inhalation exposure is significantly lower (0.03-0.06 mg/m^3) than the modelled exposure (0.08-0.34 mg/m^3). Therefore, inhalation route is not the most appropriate route of administration in the 90-day study. Oral route is the most appropriate route of administration to address systemic effects. The draft decision is amended accordingly. The Registrant also considers that the oral 90-day study is not needed for the hazard assessment. However, as the Registrant has not removed the oral 90-day testing proposal from the updated dossier, the draft decision was not amended in this respect.

In his comments to the proposals for amendments received the Registrant considered that the oral 90-day study is not needed for the hazard assessment and has removed the oral 90-day testing proposal from the updated dossier. However, since the withdrawal of the testing proposal was made so late in the process, it cannot have any effect on the current decision making. Therefore, the draft decision is not amended in this respect.

Since the substance is corrosive to skin and also inhalation exposure (e.g. by aerosol formation in metal working) cannot be excluded, there is a concern for local effects in the respiratory tract which is currently not covered in the dossier. Specifically, the measured data for inhalation exposure currently present in the dossier refers only to the manufacture of the substance. For the other exposure scenarios describing uses in the supply chain, no measured inhalation exposure information is available and modelled inhalation exposure shows that higher exposure is expected than for manufacture. Therefore, in a dossier update the Registrant will need to address any concern for local effects in the respiratory tract in relation to the potential for inhalation exposure. In case the concern cannot be clarified by other means, the Registrant should submit a testing proposal for an appropriate repeated dose toxicity study by the inhalation route.

ECHA received third party information concerning the testing proposal during the public consultation. For the reasons explained below (see section III b. Consideration of the information received during third party consultation) the information provided by third parties is not sufficient to fulfil this information requirement.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is thus required to carry out the proposed study: Oral subchronic toxicity study (90-day) (Annex IX, 8.6.2., EU method B.26.) in rat using the registered substance (dicyclohexylamine).

3. Pre-natal developmental toxicity study

Pursuant to Article 40(3)(a) of the REACH Regulation ECHA may adopt a decision requiring the Registrant to carry out the proposed test.
According to Section 8.7.2 of Annex IX of the REACH Regulation, a pre-natal developmental toxicity study is a standard requirement.

Therefore, the testing proposal for pre-natal developmental study is accepted. However, the study can be waived in case the substance is known to be a germ cell mutagen and appropriate risk management measures are implemented.

Since the Registrant is also required to carry out a mammalian spermatogonial chromosome aberration test, pre-natal developmental toxicity study should be carried out only when results of the mammalian spermatogonial chromosome aberration test are available.

ECHA received third party information concerning the testing proposal during the public

consultation. For the reasons explained below (see section III b. Consideration of the information received during third party consultation) the information provided by third parties is not sufficient to fulfil this information requirement.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Pre-natal developmental toxicity study in rats, oral route (test method: EU B.31/OECD 414) using the registered substance (dicyclohexylamine).

b) Consideration of information received during third party consultation

ECHA has further examined the scientific information submitted by third parties following the consultation in order to determine whether there is already scientifically valid information that addresses the relevant substance and hazard endpoints. This information does not, however, change the conclusion that vertebrate animal tests need to be requested, as explained below.

a) Comments concerning *in vivo* mammalian bone-marrow toxicity study: A third party proposes to evaluate the need for *in vivo* mammalian bone-marrow CA in the light of the results of the existing reproduction/developmental toxicity screening study and 28-day repeated dose toxicity study, available tests on genetic toxicity and other toxicological data. The third party considers that the proposed study cannot be justified, since there already exists prove for *in vivo* mutagenicity. The third party also considers an *in vivo* germ cell study unnecessary.

The third party has proposed a strategy for ECHA to consider before further tests on animals are requested. However, third parties were invited, as specified by Article 40(2) to submit "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal". As the proposal for a strategy as such cannot be regarded information or studies, ECHA concludes that this is not a sufficient basis for rejecting the testing proposal. However, ECHA agrees that proposed study in somatic cells is not needed. In contrast, an *in vivo* study in germ cells is necessary to elucidate the potential of the substance for germ cell mutagenicity.

b) Comments concerning oral subchronic toxicity study: The third party proposed a testing strategy:

1. To evaluate the need for 90-day study in the light of the results of the existing reproduction/developmental toxicity screening study and 28-day repeated dose toxicity study, available tests on genetic toxicity and other toxicological data.

2. Exposure considerations: use TTC for repeated dose and reproduction toxicity end points.

ECHA evaluated the comments as follows:

1. The third party has proposed a strategy for ECHA to consider. However, ECHA has invited submission of "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal", as specified by Article 40(2), and the proposal for a strategy is not "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal". Consequently, ECHA concludes that this is not a sufficient basis for rejecting the Testing Proposal. Furthermore, the dossier does not contain any data that could be used to waive the 90-day repeated dose toxicity study.

2. The third party states that since testing can be exempted based on the negligible exposure, exposure should be thoroughly analysed before conducting the test. In addition, they suggest that the Threshold of Toxicological Concern (TTC) concept should be adopted and cut-off values (human exposure threshold values below which there is no significant risk to human health) for oral (1.0 µg/kg bw/day) and inhalation (0.5 µg/kg bw/day) exposure should be used.

According to Annex XI, Section 3 of the REACH Regulation, the testing can be omitted if it can be demonstrated that there is no or no significant exposure. The Registrant did not use substance-tailored exposure-driven testing according to Annex XI, Section 3 but indicated that when working with dicyclohexylamine some inhalation and dermal exposure will occur. The exposure values are not considered to be non-significant.

Therefore, ECHA concludes that testing cannot be omitted based on negligible exposure.

c) Comments concerning pre-natal developmental toxicity study:

1. A third party has provided data on a QSAR model on prenatal developmental toxicity.

According to Annex XI, 1.3 of the REACH Regulation, the results of the QSARs may be used instead of testing when the following conditions are met: a) the results are derived from a QSAR model whose scientific validity has been established; b) the substance falls within the applicability domain of the QSAR (Quantitative/qualitative structure-activity relationship) model; c) results are adequate for the purposes of classification and labelling and/or risk assessment; and d) adequate and reliable documentation of the applied method is provided.

The evaluation of the submitted information according to the conditions described above showed that:

- The dependent variable of the model is in the form "toxic/non-toxic". In the absence of additional information on the meaning of these terms, the predicted result could not be directly used or extrapolated to fill a data gap according to the information requirements of the REACH Regulation.'
- The QSAR Model Reporting Format (QMRF) does not provide sufficient information to deduce whether the training set was constructed from studies that cover the information requirements of the OECD 414 guideline, or important study aspects, such as the species, dose selection and number of animals used. The submitted QSAR Prediction Reporting Format (QPRF) does not contain section 4 on adequacy with an interpretation of the model result in relation to the defined regulatory purpose of the Testing Proposal.
- Contrary to point b) above, based on the information in the QPRF, the possibility that the substance does not fall in the applicability domain of the model could not be ruled out. In fact, there is only evidence that the parameters of the chemical, used for prediction, fall within the ranges of the individual descriptors, used in the model. The provided QPRF contains two chemicals, which do not look similar to the registered substance.
- Contrary to point c) above, the results are not adequate for the purposes of classification and labelling and/or risk assessment, because the estimated endpoint does not have adequate and reliable coverage of the key parameters in the corresponding test method as described in the 414 OECD guideline.
- Contrary to point d) above, the level of detail in the documentation of the algorithm in the QMRF was not considered sufficient to transparently describe the model. The algorithm does not appear in the QMRF in formalised mathematical form that can be reproduced from the documentation. In addition, the training, selection and test sets

are not provided. The QMRF states that the dataset is identical to a previous version of the model, which however is not considered available.

2. A third party proposed a testing strategy:

    1. To evaluate the need for pre-natal developmental toxicity study in the light of the results of the existing reproduction/developmental toxicity screening study and 28-day repeated dose toxicity study, available tests on genetic toxicity and other toxicological data.
    2. Perform *in vitro* (pre)validated tests for the evaluation of the embryotoxic and endocrine disruption potential and apply QSAR classification models for developmental toxicity. Use results to waive developmental toxicity study.
    3. Conduct an extended One Generation Reproductive Toxicity Study (EOGRTS) and use results to waive a Two-generation Reproduction Toxicity Study and Prenatal Developmental Toxicity Study.
    4. Exposure considerations: use TTC for repeated dose and reproduction toxicity end points.

ECHA evaluated the comments as follows:

1.-2. Concerning the proposal for a strategy proposed by the third party, the conditions above (a) applies also in this case.

In addition ECHA wants to point out that the evaluation of a testing proposal is always done by ECHA in the light of other relevant data in the dossier, such as other toxicity data and exposure data. This did in this particular case not lead to the rejection of the proposal.

For in vitro tests such as mentioned by the third party the Guidance on information requirements and chemical safety assessment R.7, chapter R.7.6, states that these tests have limited value in a regulatory context.

3. Concerning the EOGRTS proposed by the third party, the reply above (c)(2) applies also in this case. In addition, it should be noted that EOGRTS cannot replace the pre-natal developmental study, since EOGRTS is not designed to detect pre-natal developmental effects.

4. Concerning the proposal for use of TTC by the third party, the conditions above (b)(2) applies also in this case.

ECHA concludes that testing cannot be omitted based on negligible exposure.

c) Deadline

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 36 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested a two-generation reproductive toxicity study. As the testing proposal for this study is not addressed in the present draft decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated IUCLID5 dossier is 24 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

IV. Adequate identification of the composition of the tested material

The process of evaluation of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the generation of information is tailored to real information needs in order to prevent unnecessary testing. The information submitted in your dossier was sufficient to confirm the identity of the substance for the purpose of assessing the testing proposal. You must note, however, that this information, or the information submitted by other registrants of the same substance, has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

In relation to the proposed tests, the sample of substance used for the new studies must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is within the specifications of the substance composition that are given by the joint registrants. It is the responsibility of all the joint registrants of the same substance to agree with the tests proposed in the testing proposal (as applicable to their tonnage level) and to document the necessary information on its composition. The substance identity information of the registered substance and of the sample tested must enable ECHA to confirm the relevance of the testing for the substance actually registered by each joint registrant. Finally, the studies must be shared by the joint registrants concerned.

V. General requirements for the generation of information and Good Laboratory Practice

ECHA always reminds registrants of the requirements of Article 13(4) of the REACH Regulation that ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP). National authorities monitoring GLP maintain lists of test facilities indicating the relevant areas of expertise of each facility.

According to Article 13(3) of the REACH Regulation, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or the European Chemicals Agency as being appropriate. Thus, the Registrant shall refer to Commission Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 as adapted to technical progress or to other international test methods recognised as being appropriate and use the applicable test methods to generate the information on the endpoints indicated above.

VI. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://echa.europa.eu/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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