EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-0000004044-84-05/F Helsinki, 25 August 2014

DECISION ON A COMPLIANCE CHECK OF A REGISTRATION PURSUANT TO ARTICLE 41(3) OF REGULATION (EC) NO 1907/2006

For 2-ethylhexylamine, CAS No 104-75-6 (EC No 203-233-8), 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 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration for 2-ethylhexylamine, CAS No 104-75-6 (EC No 203-233-8), submitted by [redacted] (Registrant). The scope of this compliance check is limited to the standard information requirements of Annex IX, Sections 8.6.2 and 8.7.2, and Annex X, Section 8.7.3 of the REACH Regulation. ECHA stresses that it has not checked the information provided by the Registrant and other joint registrants for compliance with requirements regarding the identification of the substance (Section 2 of Annex VI).

This decision is based on the registration as submitted with submission number [redacted] for the tonnage band of 1000 tonnes or more per year. This decision does not take into account any updates submitted after 6 March 2014, 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 compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

The compliance check was initiated on 4 July 2013.

On 20 September 2013 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision.

On 21 October 2013 ECHA received comments from the Registrant on the draft decision.

The ECHA Secretariat considered the Registrant's comments. The information is reflected in the Statement of Reasons (Section III) whereas no amendments to the Information Required (Section II) were made.

On 6 March 2014 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 for amendment of the draft decision within 30 days of the receipt of the notification.

Subsequently, proposals for amendment to the draft decision were submitted.

On 10 April 2014 ECHA notified the Registrant of the proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposals for amendment within 30 days of the receipt of the notification.

On 22 April 2014 ECHA referred the draft decision to the Member State Committee.

The ECHA Secretariat reviewed the proposals for amendment received and modified section III of the draft decision.

The draft decision was split into two draft decision documents: one relating to the request for a two-generation reproductive toxicity study and one relating to the request for a sub-chronic toxicity study (90-day) and a pre-natal developmental toxicity study.

The present decision relates solely to compliance checks for a sub-chronic toxicity study (90-day) and a pre-natal developmental toxicity study. The other compliance check requirement of a two-generation reproductive toxicity study (Annex X, 8.7.3.; test method: EU B.35./OECD 416) in rats, oral route is addressed in a separate decision although all endpoints were initially addressed together in the same draft decision.

By 12 May 2014 in accordance to Article 51(5), the Registrant provided comments on the proposals for amendment. The Member State Committee took the comments of the Registrant on the proposal(s) for amendment into account.

A unanimous agreement of the Member State Committee on the draft decision relating to sub-chronic toxicity study and a pre-natal developmental toxicity study was reached on 26 May 2014 in a written procedure launched on 15 May 2014. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Information required

Pursuant to Articles 41(1), 41(3), 10(a)(vii), 12(1)(e), 13 and Annexes IX and X of the REACH Regulation the Registrant shall submit the following information using the indicated test methods and the registered substance subject to the present decision:

1. Sub-chronic toxicity study (90-day), inhalation route (Annex IX, 8.6.2.; test method: OECD 413) in rats;

2. Pre-natal developmental toxicity study (Annex IX, 8.7.2.; test method: EU B.31./OECD 414) in rats or rabbits, oral route.

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated registration to ECHA by **1 September 2016.** The timeline has been set to allow for sequential testing as appropriate.

III. Statement of reasons

Pursuant to Article 41(3) of the REACH Regulation, ECHA may require the Registrant to submit any information needed to bring the registration into compliance with the relevant information requirements.

Pursuant to Articles 10(a)(vii), 12(1)(e) of the REACH Regulation, a technical dossier for a substance manufactured or imported by the Registrant in quantities of 1000 tonnes or more per year shall contain as a minimum the information specified in Annexes IX and X of the REACH Regulation.

1. Sub-chronic toxicity study (90-day), inhalation route (Annex IX, 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.

The Registrant has not provided any study record of a sub-chronic repeated dose toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.6.2. Instead, the Registrant has provided a Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422) with the read-across substance octylamine hydrochloride (CAS 142-95-0, EC 205-574-8). A Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test can however not replace a sub-chronic toxicity study, because, amongst other reasons, the administration period is considerably shorter than for a sub-chronic toxicity study (typically 56 days versus 90 days), without prejudice of the validity of the RA which was not assessed by ECHA at this stage.

As explained above, the information available 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.

In their general comments the Registrant explained their approach to cover the Annex VIII requirements using read-across to a structural similar compound with the read-across substance Octylamine-hydrochloride and to waive Annex IX and X requirements for exposure considerations, using the available read-across data to derive a DNEL and demonstrate safe use for the registered industrial and professional uses. The Registrant also pointed out that the registered substance is part of the OECD SIDS category "C1-C13 Primary Amines" for which further testing was not expected to be required.

ECHA notes that pursuant to Annex XI, Section 3.2. of the REACH Regulation, in order to apply an exposure based adaptation, the Registrant has to provide adequate justification and documentation which is not present in this dossier. Moreover, the DNEL derived by the Registrant from a Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422) on the read-across substance octylamine hydrochloride (CAS 142-95-0, EC 205-574-8) shall not be considered appropriate to omit a 90-day repeated dose toxicity study, as the Registrant did not fulfil the criteria of Annex XI, Section 3.2(a)(ii) footnote (1), without prejudice of the validity of the read-across. The read-across was not assessed by ECHA at this stage, because the submitted study does not fulfil the requirements of the respective endpoints, regardless whether the study was performed with the registered substance or a read-across substance. With reference to the OECD SIDS programme ECHA notes that conclusions made in that programme are not necessarily the same as the conclusions to be drawn according to the REACH Regulation.

In their endpoint specific comments the Registrant proposed including additional parameters to assess fertility (i.e. sperm motility). ECHA notes that the proposed investigation of additional parameters may contribute to a weight of evidence approach, but cannot serve as a valid replacement for a two-generation reproductive toxicity study.

In light of the physico-chemical properties of the substance (liquid classified as corrosive to the skin and damaging to the eyes) and the information provided on the uses and human exposure (uses with spray application and by brushing, dipping and pouring in concentrations of the substance up to [redacted] ECHA considers that testing by the inhalation route is most appropriate.

In their general comments, the Registrant additionally sought to justify the proposal for adaptation based on corrosiveness of the substance and high acute toxicity via inhalation route. ECHA interprets the proposal as a reference to the fourth introductory paragraph 4 of Annex IX of the REACH Regulation according to which "in vivo testing with corrosive substances at concentration/dose levels causing corrosivity shall be avoided".
However, ECHA would like to point out that according to the text of the relevant provision the above mentioned text implies that substances quoted above non-corrosive concentration(s) can be tested. Introductory paragraph 4 is not a legal basis for adapting standard information requirements. The general principle of adjusting the concentration of the test substance to avoid corrosion and irritation is set out in the relevant test guidelines, for example, in OECD Test Guideline 413, paragraph 4. ECHA is of the opinion that the registered substance can thus be tested.

According to the test method OECD 413 the rat is the preferred rodent species. ECHA considers this species as being appropriate

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: Sub-chronic inhalation toxicity: 90-day study (test method: OECD 413) in rats.

2. Pre-natal developmental toxicity study (Annex IX, 8.7.2.)

A "Pre-natal developmental toxicity study" 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.

The Registrant has not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2.

Instead, the Registrant has sought to adapt the information requirement for a prenatal developmental toxicity study (Annex IX, 8.7.2.). The Registrant has justified the proposal for adaptation as follows:

"(1) Results of the exposure assessment cover all relevant exposures throughout the life cycle of the substance and demonstrate the absence of significant exposure in all scenarios of the manufacture and all identified uses as referred to in Annex VI section 3.5; the uses clearly demonstrate that there is no chronic exposure and no wide dispersive use for both the worker and the Consumer. Industrial workers can at maximum be exposed acutely and short-term as the substance is used in closed systems as the substance is highly corrosive (R35) and toxic if inhaled (T, R23); The main part of the substance is used as an Intermediate and Monomer. (2) DNELs for short-term exposure and longterm-exposure have been derived from results of available test for Ethylhexylamine CAS 104-75-6 and for the structural analogue Octylamine CAS 111-86-4 where the salt was tested via gavage in a combined Reproductive Toxicity Screen and 28-days repeated Dose Toxicity Study (OECD 422). No adverse effects were obsersed neither on reproduction nor on fertility. The derived

DNEL is relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes (3) the comparison of the derived DNEL with the results of the exposure assessment shows that exposures are always well below the derived DNEL. Thus the industrial use is safe for the worker and there is no chronic exposure. The combined risk characterization ratios (RCR combined) are < 1."

The Registrant has justified the proposal for adaptation with a reference to "exposure conditions" in IUCLID Section 7.8.2. Furthermore, the Registrant has referred to Annex XI, section 3. It is the understanding of ECHA that the Registrant claims that all of the three conditions of Annex XI, section 3.2.(a) are fulfilled, i.e. that:
(i) the results of the exposure assessment covering all relevant exposures throughout the life cycle of the substance demonstrate the absence of or no significant exposure in all scenarios of the manufacture and all identified uses as referred to in Annex VI section 3.5;
(ii) a DNEL can be derived from results of available data for the substance concerned taking full account of the increased uncertainty resulting from the omission of the information requirement, and that DNEL is relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes;
(iii) the comparison of the derived DNEL with the results of the exposure assessment shows that exposures are always well below the derived DNEL.

In this respect, pursuant to Annex XI, Section 3.2. of the REACH Regulation, in order to apply an exposure based adaptation, the Registrant has to provide adequate justification and documentation. Moreover, pursuant to Section 3.2(a)(ii) footnote 1 of Annex XI, the Registrant has to take into account that a DNEL derived from a screening test for reproductive/developmental toxicity shall not be considered appropriate to omit a prenatal developmental study.

The Registrant has however derived the DNEL from a Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422) on the read-across substance octylamine hydrochloride (CAS 142-95-0, EC 205-574-8). The DNEL so derived is thus not appropriate to omit a prenatal developmental toxicity study, as the Registrant did not fulfill the criteria of Annex XI, Section 3.2(a)(ii) footnote (1), without prejudice of the validity of the read-across which was not assessed by ECHA at this stage As explained above, the information available 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.

In addition to the general comments presented already under section III.1 above, the Registrant proposed to perform the pre-natal developmental toxicity study in rats as the first species and via the inhalation route of administration.

ECHA notes that reproductive toxicity studies are intended to provide hazard information on reproductive toxicity in addition to other systemic toxic effects, to contribute to risk assessment and to provide a basis for classification and labelling. Therefore, in reproductive toxicity studies it is considered more important to achieve sufficiently high systemic exposure (i.e. ensure hazard identification) than to mimic actual human exposure conditions. An important mean to achieve sufficiently high exposure is the selection of the route of administration. For this substance, the corrosive properties will be a limiting factor for inhalation studies.

According to the toxicological data for the registered substance the 48h/LC100 (inhalation route) was about 1.5 mg/L and deaths occurred between 40 and 177 minutes after start of the exposure, corresponding to LD100 values between about 62 and 274 mg per kg body weight (12 L inhaled air per hour for rats with a body weight of 200 g). An acute oral toxicity study resulted in an LD50 of 316 mg per kg body weight, and an LD100 of 632 mg per kg body weight. It can thus be concluded that considerably higher systemic exposure can be achieved via the oral route of administration, which is thus the most appropriate route of administration. Concerning the Registrant's comment on the test species, ECHA notes that the Registrant is given the choice for the first species to be tested.

According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is 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 414) in rats or rabbits by the oral route.

Note for consideration by the Registrant:

In addition, a pre-natal developmental toxicity study on a second species is part of the standard information requirements as laid down in Annex X, section 8.7.2. for substances registered for 1000 tonnes or more per year (see sentence 2 of introductory paragraph 2 of Annex X).

The Registrant should firstly take into account the outcome of the pre-natal developmental toxicity on a first species and all other relevant available data to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI; for example if the substance meets the criteria for classification as toxic for reproduction Category 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, or alternatively, if weight of evidence assessment of all relevant available data provides scientific justification that the study in a second species is not needed. If the Registrant considers that the conditions for these adaptations are not fulfilled, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species. If the Registrant comes to the conclusion that the conditions for these adaptations can be fulfilled, he should update his technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex X, 8.7.2. of the REACH Regulation.

In addition to the general comments presented already under section III.1 above, the Registrant proposed to decide on the need for a pre-natal developmental toxicity study on a second species after results of the first species become available.

ECHA however notes that ECHA did not request a pre-natal developmental toxicity study in the second species in its draft decision and that ECHA has already included in the statement of reasons of the draft decision detailed legal and scientific considerations on which data should be taken into account to determine if the conditions are met for adaptations according to Annex X, 8.7. column 2, or according to Annex XI.

3. Deadline for submitting the information

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 (Annex X, 8.7.3.). As this endpoint is not addressed in the present decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated registration 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

ECHA stresses that the information submitted by the Registrant and other joint registrants for identifying the substance has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

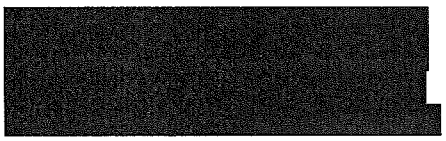
In relation to the information required by the present decision, the sample of substance used for the new studies must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is within the specifications of the substance composition that are given by the joint registrants. It is the responsibility of all 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 substance tested in the new studies 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 by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new studies 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 studies to be assessed.

V. 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 an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on 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.



Leena Ylä-Mononen
Director of Evaluation