ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000002159-73-05/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 1-Hexanol, 2-ethyl-, manuf. of, by-products from, distn. residues, CAS No 68609-68-7 (EC No 271-832-1), 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 1-Hexanol, 2-ethyl-, manuf. of, by-products from, distn. residues, CAS No 68609-68-7 (EC No 271-832-1), submitted by [redacted] (Registrant).

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band of 1 to 10 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.

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

- An extended developmental toxicity study which includes prolonged pre-treatment and examination of relevant parameters of a 90-day study and fertility parameters, to fulfil the information requirements for a sub-chronic toxicity study (90-day), pre-natal developmental toxicity study and two-generation reproductive toxicity study.

Members of the joint submission for which the Registrant acts as lead Registrant registered at a tonnage band >1000 tonnes per annum, i.e. a tonnage level where the data requirements meant to be covered by the proposed test have to be met. There is a necessity to generate the data to cover the above-mentioned endpoints in order to be compliant with the information requirements of the REACH Regulation at a tonnage band >1000 tonnes per annum, at least for members of the joint submission.

The present decision relates to the examination of the testing proposals for a sub-chronic toxicity study (90-day) study and a 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 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 registration at a later stage.

The examination of the testing proposals was initiated on 23 September 2010.

ECHA opened a third party consultation for the testing proposals including testing on vertebrate animals that was held from 15 July 2011 until 29 August 2011. ECHA did receive information from third parties (see section III below).

On 2 December 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.

On 2 January 2012 ECHA received comments from the Registrant.

ECHA considered the Registrant's comments received and amended the draft decision. The comments are reflected in the Statement of Reasons (Section III) whereas no amendment to the Testing required (Section II) was made.

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 21 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 proposal for a sub-chronic toxicity study (90-day) study and a pre-natal developmental toxicity study.

A unanimous agreement of the Member State Committee on the draft decision relating to the testing proposal for a sub-chronic toxicity study (90-day) study and a pre-natal developmental toxicity study was reached on 8 October 2012 in a written procedure launched on 26 September 2012 and ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Testing required

Pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant shall carry out the following tests using the indicated test methods and the registered substance concerned by the present draft decision:

1. Pre-natal developmental toxicity study in rats or rabbits, oral route (Annex IX, 8.7.2., test method: EU B.31/OECD 414);
2. Sub-chronic toxicity study (90-day) in rats, oral route (Annex IX, 8.6.2., test method: EU B.26/OECD 408);

while the originally proposed test "An extended developmental toxicity study which includes prolonged pre-treatment and examination of relevant parameters of a 90-day study and fertility parameters, to fulfil the information requirements for a sub-chronic toxicity study (90-day), pre-natal developmental toxicity study and two-generation reproductive toxicity study." - as clarified by the comments provided by the Registrant - is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

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 the column 2 provisions of the respective Annex and those contained in Annex XI 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.

Data from a second pre-natal developmental toxicity study on another species is a standard information requirement according to Annex X, 8.7.2. of the REACH Regulation. 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. If the Registrant considers that testing is necessary to fulfill this information requirement, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species.

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 submitted by the Registrant for the registered substance and scientific information submitted by third parties.

1. Pre-natal developmental toxicity

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject the proposed test and require the Registrant to carry out other tests than the one proposed in case of non compliance of the proposed test.

Pre-natal developmental toxicity studies are part of the standard information requirements as laid down in Annexes IX and X, section 8.7.2. 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 Registrant in his registration dossier proposed to fulfil the information requirement for this endpoint by performing an "extended developmental toxicity study which includes prolonged pre-treatment and examination of relevant repeated dose toxicity and fertility parameters" according to method OECD 414 (prenatal developmental toxicity study).

In his comments on the draft decision, the Registrant provided a clarification regarding his original testing proposal submitted in the registration dossier.
The Registrant acknowledged that the wording of the initial testing proposal was misleading as not an extended developmental toxicity study but an "extensible OECD 415" (extensible one-generation study) was suggested. The proposed study should not be confused with the extended one-generation study test protocol (OECD 443). The basis of the testing proposal has been a modification of the proposed design of the US National Toxicology Program (NTP) of a "modified one-generation reproduction study". According to the Registrant, this NTP design covers cohorts for which essentially the same test protocols are used as for individual standard studies and would include:

- a sub-chronic toxicity cohort to evaluate target organ toxicity, pathology, clinical pathology comparable to the OECD 408 test protocol,
- a teratology cohort to evaluate prenatal developmental toxicity comparable to the OECD 414 test protocol,
- a littering cohort to evaluate reproductive performance as well as evaluation of the F1 animals (extensible OECD 415) with the possibility to proceed to the F2 generation if needed (triggers may be seen in parental and/or offspring reproductive findings).

Furthermore, in his comments on the draft decision, the Registrant also proposed a refined testing approach, including a tiered testing strategy to evaluate the toxicological endpoints of concern especially to decide whether testing of reproductive toxicity (fertility) is needed or not.

The Registrant stated that this "extensible OECD 415 method", a modification of the NTP modified one generation reproduction study, would fulfil the conditions under section 1.1.2 of Annex XI for pre-natal developmental toxicity, sub-chronic toxicity (90-day) and the two-generation reproductive toxicity. No further details of the proposed modification of the study design were provided. However, ECHA considers that based on the clarification of the proposed test submitted, the Registrant does not show that the proposed "extensible OECD 415" design would fulfil the information requirements of the present endpoint (or the other two endpoints addressed by this decision) or the conditions of Annex XI, 1.1.2. It should be noted that the conditions specified under section 1.1.2 of Annex XI refer to existing studies, not to studies that are to be performed. In addition, the modified "NTP modified one-generation study" is not an internationally accepted study referred in Article 13(3) of REACH.

With regard to pre-natal developmental toxicity, although most of the parameters examined in the NTP modified one-generation study protocol appear to be similar to the ones examined according to the EU B.31/OECD 414 method, there is a remarkable difference in the exposure period and number of animals tested. According to the NTP modified one-generation study protocol, the prenatal toxicology cohort is conducted using F1 animals and dams are exposed already before mating while according to the EU B.31/OECD 414 method, the exposure starts after implantation. This has an impact on the possibility to select the most appropriate dose levels. Both the exposure duration and dose level selection may hamper the interpretation of the results by making the distinction between the

developmental effects and other systemic effects more difficult, and affect the need for classification. Furthermore, the NTP modified one-generation study protocol foresees the use of 20 animals, while the EU B.31/OECD 414 method requires the use of 20 pregnant animals.

Therefore ECHA rejects the clarified testing proposal of the Registrant in accordance with Article 40(3) (d) of the REACH Regulation with regard to the present endpoint as the proposed test is incompliant with the requirements of the REACH Regulation.

ECHA notes that in his testing proposal, the Registrant did not provide any justification for the adaptation of the standard information requirements/testing related to exposure considerations/use of risk management measures, based on either Column 2 of Annex IX and X or based on Annex XI. Furthermore, the available information on the substance's intrinsic properties (the substance is classified for skin irritation) and exposure do not show that the conditions in column 2 of Annex IX and X or Annex XI would be met. In the official comments, the Registrant is making some exposure considerations and is also referring to a recent analysis of exposure with a more realistic tier 2 assessment tool. However, he does not provide any further details on this analysis or exposure values. As regards exposure-based adaptation of the standard information requirements, it should be noted that the conditions laid down in section 3.2. (a) (ii) of Annex XI stipulate that for repeated dose toxicity tests or reproductive toxicity tests, a derived no effect level (DNEL) derived from a lower tier test is not considered appropriate to omit the respective higher tier studies. According to section 3.2 (b) of Annex XI, exposure based adaptation may be used to omit such studies provided that the Registrant demonstrates that strictly controlled conditions as described in Article 18(4)(a) to (f) apply to the substance. The Registrant did not show in the registration dossier or the comments provided that there is no or no significant exposure or that the strictly controlled conditions for the whole life-cycle of the substance apply. ECHA therefore concludes that adaptation of the standard information requirements subject to this draft decision is not justified either based on points 3.2. (a) or 3.2. (b) of Annex XI.

Furthermore, in his comments on the draft decision, the Registrant also proposed **a refined testing approach**, including a tiered testing strategy to evaluate the toxicological endpoints of concern especially to decide whether testing of reproductive toxicity (fertility) is needed or not. As part of this testing strategy, the Registrant agreed to perform the Pre-natal developmental toxicity study in rats, oral route (test method: EU B.31/OECD 414). Further details of the proposed refined testing proposal are addressed in section 2 and 3 below.

The Registrant did not specify the species and route to be used for testing. 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. In the light of the physico-chemical properties of the substance and the information provided on the uses and human exposure ECHA considers these default parameters appropriate and testing should be performed by the oral route, with the rat as a first species to be used.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is required to carry out the following study: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414) using the registered substance.
When considering the need for a testing proposal for a prenatal developmental toxicity study in a second species, the Registrant should take into account the outcome of the pre-natal developmental toxicity study on the first species and all 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.

2. Sub-chronic toxicity (90-day)

a) Examination of the testing proposal

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject the proposed test and require the Registrant to carry out one or more additional tests in case of non-compliance of the testing proposal with Annexes IX, X and XI of the REACH 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. 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 generate the data for this endpoint.

The Registrant in his registration dossier proposed to fulfil this information requirement by performing "*an extended developmental toxicity study which includes prolonged pre-treatment and examination of relevant parameters of a 90-day study*" and applying a method equivalent or similar to OECD guideline 408 (Repeated dose 90-day oral toxicity in rodents). Based on the clarification of the testing proposal that was submitted as comment on the draft decision it became clear that the Registrant's testing proposal did not include a 90-day repeated dose toxicity study according to OECD guideline 408, but that the information requirement of Annex IX, section 8.6.2. of the REACH Regulation was intended to be filled by the "extensible OECD 415", based on a modified "NTP modified one-generation" protocol, which includes a "sub-chronic toxicity cohort to evaluate target organ toxicity, pathology, clinical pathology comparable to the OECD 408 test protocol", as explained in Section III. 1 above according to the Registrant. However, the Registrant has not demonstrated how the proposed NTP modified one-generation study would generate information that would be provided by a standard sub-chronic toxicity study (90 day).

According to the NTP modified one-generation protocol, the animals are exposed already *in utero*, while according to the OECD 408 the exposure starts after weaning using young adults. This has an impact on the possibility to select the most appropriate dose levels. Furthermore it may also hamper the interpretation of the study results in sense of separating the developmental effects from other systemic effects. Therefore, the proposed method does not meet the Annex IX, section 8.6.2 of the REACH Regulation for a sub-chronic toxicity study (90-day) and ECHA rejects the clarified testing proposal of the Registrant in accordance with Article 40(3)(d) of the REACH Regulation with regard to the present endpoint as the proposed test is incompliant with the requirements of the REACH Regulation .

Concerning the adaptation of standard information requirements related to exposure considerations that the Registrant included in the comments on the draft decision, ECHA has the same considerations as explained in Section III.1. above.

In his comments on the draft decision, as part of the **refined testing approach**, mentioned in section III.1 above, the Registrant agreed to perform the repeated dose 90-day oral toxicity in rodents (EU B.26/OECD guideline 408). The Registrant also proposed to extend this study by including additional examinations/parameters i.e. spermatogenesis (testicular histopathology), sperm production and sperm integrity/function, oestrus cycle, follicle counts. ECHA notes, that it is at the Registrant's discretion to perform the intended

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additional examinations during the testing program and use the results to ensure the safe use of the substance. However, the Registrant is reminded that the proposed extension of this study does not fulfil the standard information requirements in the registration dossier for reproductive toxicity set out in Annex X, 8.7.3., unless Annex X, 8.7., column 2 adaptation is applied and justified.

In the light of the physico-chemical properties of the substance and the information provided on the uses and human exposure, ECHA considers that testing by the oral route is appropriate.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is required to carry out the following study: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD 408) using the registered substance.

b) Consideration of third party information

ECHA received third party information concerning the testing proposal during the public consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

The third party provided results of a 3 weeks study (method not specified) with the substance 2-ethylhexanal.

However, a three week study does not cover the study duration of sub-chronic 90-day toxicity study (test method: EU B.26/OECD 408). Furthermore, the study cited by the third party cannot be evaluated by ECHA as insufficient information is provided in this secondary citation. In addition, the read-across justification provided by the third party is not robust enough to allow the conclusion that the requirements of Annex XI 1.5. are met. Therefore ECHA concludes that this is not sufficient basis to fulfil the information requirement.

4. Deadline of the decision

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 according to the standard information requirement of Annex X, 8.7.3 of the REACH Regulation. 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 new studies meet real information needs. Within this context, the Registrant's dossier was sufficient to confirm the identity of the substance to the extent necessary for evaluation of the testing proposal. The Registrant 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.

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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 joint registrants of the same substance to agree to the tests proposed (as applicable to their tonnage level) 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 grades registered to enable the relevance of the studies to be assessed.

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

ECHA 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).

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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