EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-2114299628-28-01/F Helsinki, 12 June 2015

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

**For bis(2-ethylhexyl) peroxydicarbonate, CAS No 16111-62-9 (EC No 240-282-4 ), 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 the following testing proposals submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(d)thereof for bis(2-ethylhexyl) peroxydicarbonate, CAS No 16111-62-9 (EC No 240-282-4, submitted by [redacted] (Registrant).

- 90-day oral toxicity study (OECD 408).
- Developmental toxicity / teratogenicity study (OECD 414) in rats.

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 5 March 2015, 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 registration at a later stage.

ECHA received the updated registration dossier containing the above-mentioned testing proposals for further examination pursuant to Article 40(1) on 24 February 2014.

ECHA held a third party consultation for the testing proposals from 15 April 2014 until 30 May 2014. ECHA received information from third parties (see section III below).

On 14 November 2014 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 22 December 2014 ECHA received comments from the Registrant on the draft decision.

The ECHA Secretariat considered the Registrant's comments. On basis of this information, only the deadline in Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

On 5 March 2015 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.

As no proposal for amendment was submitted, ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

## II. Testing required

### A. Tests required pursuant to Article 40(3)

The Registrant shall carry out the following proposed test with modifications pursuant to Article 40(3)(b) and 13(4) of the REACH Regulation using the indicated test method and the registered substance subject to the present decision:

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26/OECD 408) in rats modified to include urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy.

   It is at the Registrant's discretion to perform the intended additional reproductive examinations during the testing program.

The Registrant shall carry out the following proposed test pursuant to Article 40(3)(a) and 13(4) of the REACH Regulation using the indicated test method and the registered substance subject to the present decision:

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

Note for consideration by the Registrant:

The Registrant 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 to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation.

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 the Member States.

### B. Deadline for submitting the required information

Pursuant to Articles 40(4) and 22(2) of the REACH Regulation, the Registrant shall submit to ECHA by **19 June 2017** an update of the registration dossier containing the information required by this decision, including, where relevant, an update of the Chemical Safety Report. The timeline has been set to allow for sequential testing as appropriate.

III. Statement of reasons

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

A. Tests required pursuant to Article 40(3)

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)

a) Examination of the testing proposal

Pursuant to Article 40(3)(b) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test under modified conditions.

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 Registrant has submitted a testing proposal for a sub-chronic toxicity study (90 day) via the oral route (EU B.26/OECD 408).

ECHA considers that the proposed study via oral route is appropriate to fulfil the information requirement of Annex IX, Section 8.6.2. of the REACH Regulation.

The Registrant proposed testing by the oral route. In light of the physico-chemical properties of the substance (liquid with low vapour pressure), the available oral 28-day study indicating a concern for systemic toxicity that requires further information on repeated dose toxicity by the oral routeECHA considers that testing by the oral route is the most appropriate route.

The Registrant did not specify the species to be used for testing. According to the test method EU B.26/OECD 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

The Registrant proposed to extend the sub-chronic toxicity study (90 day) by including additional examinations and parameters (*histopathology of the testes, as well as weights of reproductive organs and accessory glands (i. e. testis, epididymis, prostate, seminal vesicle*)). ECHA notes that it is at the Registrant's discretion to perform the intended 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 would not itself fulfil the standard information requirements in the registration dossier for reproductive toxicity set out in Annex IX, Section 8.7.3. unless the Registrant applies the results from the 90-day study as a valid adaptation according to Annex IX, Section 8.7, column 2.

In the 28-day repeated dose toxicity study, hyaline droplets in corticotubular cells, considered to represent α2-microglobulin, were seen in a dose-related manner at 500 and 1000 mg/kg/day. They were associated with a minimal increase in cortical basophilic tubules in both dose groups and with minimal numbers of debris-filled tubules in the inner cortex at 1000 mg/kg/day were observed in male rats. The fact that these effects were only observed in the kidneys of male rats indicates that the registered substance may induce alpha-2u-globulin-mediated nephropathy. Since humans do not excrete alpha-2u-globulin, this mode of action is not relevant to humans. For this reason, ECHA decided to modify the

Registrant's testing proposal by including urinalysis (which is optional in paragraph 30 of OECD 408, and the relevant part of Section 1.5.2.2. of EU Method B.26) to investigate kidney function, and a full histopathological examination (paragraph 36 of OECD 408, Section 1.5.2.4. of EU Method B.26), which is to include immunohistochemical investigation of renal pathology to determine if the pathology is indeed mediated by alpha-2u globulin.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation.

A third party has proposed the following read-across approach: "The registered chemical is characterized by a peroxy dicarbonate structure which hydrolyses instantly in aqueous solutions. Therefore, the parent compound will not be systemically bioavailable after oral ingestion. The hydrolysis product 2-ethylhexan-1-ol has been registered with a guideline compliant oral sub-chronic toxicity study in the rat. Target organs of repeated dose toxicity were the liver, kidneys, and the forestomach due to irritation properties. These data obtained with the hydrolysis product 2-ethylhexan-1-ol seem to be an appropriate key study for the registration of the parent compound in a read-across approach."

ECHA acknowledges that the third party has proposed a testing strategy including a read across approach for the Registrant to consider.

ECHA notes that the information provided by the third party is currently insufficient for demonstrating that the conditions of Annex XI, Section 1.5. of the REACH Regulation are met since insufficient data has been submitted to support the proposed read-across approach. Therefore, the information provided by the third party in itself would not be sufficient to adapt the standard information requirement.

ECHA notes that it is the Registrant's responsibility to consider and justify any adaptation of the information requirements in accordance with the relevant conditions as established in Annex XI, Section 1.5. Therefore, the Registrant should assess whether he can justify a read-across as suggested by the third party. If the adaptation can be justified, he should include the adaptation argument with all necessary documentation in an update to the registration dossier. Such an update can only be taken into consideration in the decision-making if it is submitted before the draft decision is sent to the Member State Competent Authorities pursuant to Article 51(1) of the REACH Regulation.

c) Outcome

Therefore, pursuant to Article 40(3)(b) of the REACH Regulation, the Registrant is requested to carry out the proposed study with modifications as detailed in section a) above with the registered substance subject to the present decision: Sub-chronic toxicity study (90-day) in rats, oral route (test method: EU B.26/OECD 408).

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

a) Examination of the testing proposal

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

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. 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 has submitted a testing proposal for a pre-natal developmental toxicity study in rats according to EU B.31/OECD 414.

ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

The Registrant proposed testing in rats. He did not specify the route 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. 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.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation.

A third party has proposed the following read-across approach: "The registered chemical is characterized by a peroxy dicarbonate structure which hydrolyses instantly in aqueous solutions. Therefore, the parent compound will not be systemically bioavailable after oral ingestion. The hydrolysis product 2-ethylhexan-1-ol has been registered with published reliable oral, dermal and inhalation pre-natal developmental toxicity studies in the rat. These data obtained with the hydrolysis product 2-ethylhexan-1-ol seem to be an appropriate key studies for the registration of the parent compound in a read-across approach."

ECHA acknowledges that the third party has proposed a testing strategy including a read across approach for the Registrant to consider.

ECHA notes that the information provided by the third party is currently insufficient for demonstrating that the conditions of Annex XI, Section 1.5. of the REACH Regulation are met since insufficient data has been submitted to support the proposed read-across approach. Therefore, the information provided by the third party in itself would not be sufficient to adapt the standard information requirement.

ECHA notes that it is the Registrant's responsibility to consider and justify any adaptation of the information requirements in accordance with the relevant conditions as established in Annex XI, Section 1.5. Therefore, the Registrant should assess whether he can justify a read-across as suggested by the third party. If the adaptation can be justified, he should include the adaptation argument with all necessary documentation in an update to the registration dossier. Such an update can only be taken into consideration in the decision-making if it is submitted before the draft decision is sent to the Member State Competent Authorities pursuant to Article 51(1) of the REACH Regulation.

c) Outcome

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

B. Deadline for submitting the required information

In the draft decision communicated to the Registrant the time indicated to provide the requested information was 18 months from the date of adoption of the decision. In his comments on the draft decision of 12 December 2014, the Registrant requested an extension of the timeline to 24 months. He claimed limited laboratory capacities in Europe especially for the two respective study types. ECHA considered the registrant's comment and extended the deadline for submitting the information to 24 months.

IV. Adequate identification of the composition of the tested material

The process of examination 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 examination of the testing proposal.

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 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 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://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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