ECHA
EUROPEAN CHEMICALS AGENCY

Decision number : TPE-D-0000002946-64-04/F Helsinki, 17 June 2013

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

For [1,3(or 1,4)-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide, CAS No 25155-25-3 (EC No 246-678-3), 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 proposal submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(e) thereof for [1,3(or 1,4)-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide, CAS No 25155-25-3 (EC No 246-678-3), by [redacted] (Registrant).

- 90-day oral toxicity study (OECD 408) in rats, oral route
- Developmental toxicity / teratogenicity study (OECD 414)
- Toxicity to aquatic invertebrates: Daphnia magna reproduction test (OECD 211)
- Bioaccumulation in aquatic/sediment: Fish dietary test
- Sediment toxicity: Sediment-water Chironomid toxicity using spiked sediment (OECD 218)
- Biodegradation in water and sediment: aerobic and anaerobic transformation in aquatic sediment systems (OECD 308)

This decision is based on the registration dossier 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 after 2 November 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 registration at a later stage.

On 22 October 2010, pursuant to Article 40(1) of the REACH Regulation, ECHA initiated the examination of the testing proposal set out by the Registrant in the registration dossier for the substance mentioned above.

ECHA held a third party consultation for the testing proposal from 6 March 2012 until 20 April 2012. ECHA did not receive information from third parties.

On 9 August 2012 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 August 2012 ECHA received comments from the Registrant. On 2 August 2012 the Registrant had updated his registration dossier and removed the testing proposals for Bioaccumulation in aquatic/sediment and Biodegradation in water and sediment.

ECHA considered the Registrant's comments received and the updated registration dossier. On this basis, section II was amended by removing the tests for Bioaccumulation in aquatic/sediment and Biodegradation in water and sediment. The Statement of Reasons (Section III) was changed accordingly.

On 2 November 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, one Competent Authority of a Member State submitted a proposal for amendment to the draft decision.

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

ECHA reviewed the proposal for amendment received and decided not to amend the draft decision.

On 17 December 2012 ECHA referred the draft decision to the Member State Committee.

On 19 December 2012 the Registrant provided comments on the proposed amendments. The Member State Committee took the comments of the Registrant into account.

After discussion in the Member State Committee meeting on 5-7 February 2013, a unanimous agreement of the Member State Committee on the draft decision was reached on 5 February 2013. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Testing required

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

1. Pre-natal developmental toxicity study in rats, oral route (Annex IX, 8.7.2.; test method: EU B.31/OECD 414).
2. Long-term toxicity testing on aquatic invertebrates (Annex IX, 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211).
3. Long-term toxicity to sediment organisms (Annex X, 9.5.1.; test method: Sediment-water Chironomid toxicity using spiked sediment, OECD 218);

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

4. Sub-chronic toxicity study (90-day) in rats, oral route (Annex IX, 8.6.2.; test method: EU B.26/OECD 408). The study protocol shall be modified with additional urinalysis to characterise kidney toxicity, and full renal histopathology will include immunohistochemical determination of alpha-2u globulin, to evaluate whether there is an alpha-2u mode of action, specifically as provided for in OECD 408, paragraphs 30, 32 and 36.

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 **17 June 2015** 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 proposals submitted by the Registrant for the registered substance.

1. Pre-natal developmental toxicity study

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.

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 as a first species to be used.

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.

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. Long-term toxicity testing on aquatic invertebrates

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

According to column 1 of Section 9.1.5 of Annex IX of the REACH Regulation, long-term toxicity testing on invertebrates is required to fulfil the standard information requirements. 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 provided the following justification for conducting the proposed test: "According to claimed uses of [1,3(or 1,4)-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide aquatic compartment exposure is likely. At the moment no data is available for characterizing [1,3(or 1,4)-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide long-term effects on organisms inhabiting aquatic compartment. Risk assessment demonstrated that there is no risk for those organisms using the PNEC derived based upon acute data, however a long-term test on aquatic invertebrates is proposed for in order to refine the PNEC value".

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Long-term toxicity testing on aquatic invertebrates (Annex IX, 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211) using the registered substance.

ECHA notes that from the information available in the technical dossier, it is difficult to establish the sensitivity on the registered substance as the acute fish study was performed on a read across substance, "1,3-bis[1-(tert-butylperoxy)-1-methylethyl]benzene due to structural analogy.

Therefore, once results of the proposed test on long-term toxicity to aquatic invertebrates are available, the Registrant shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation. If the revised chemical safety assessment indicates the need to investigate further the effects on aquatic organisms, the Registrant should submit a testing proposal for a long-term toxicity test on fish in order to fulfil the standard information requirement of Annex IX, 9.1.6. If the Registrant comes to the conclusion that no further investigation of effects on aquatic organisms is required, he should update his technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex IX, 9.1.6.

3. Long-term toxicity testing on sediment organisms

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

According to column 1 of Section 9.5.1 of Annex X of the REACH Regulation, long-term toxicity to sediment organisms is a standard information requirement. 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 proposed a sediment-water Chironomid toxicity test using spiked sediment (OECD 218).

The Registrant provided the following justification for conducting the proposed test:

> *"Sediment and water compartments exposition is likely. Besides, based upon the adsorption potential of the substance of interest, toxicity tests would be recommended and so are proposed in order to get more information of the effect of the concerned substance on the organisms living in the sediment compartment. These tests will permit to improve the PNEC value for sediments even if at the moment no risk has been identified."*

The substance is adsorptive (logKoc range from 3.1 to 4.8) and exposure to sediment cannot be excluded. Therefore, potential long-term effects to the sediment should be investigated.

The information currently available in the dossier is not considered as sufficient to conclude on the long-term toxicity potential of the registered substance in sediment organisms and thus it is necessary to generate additional data for this endpoint.

ECHA notes that from the information available in the technical dossier, the Registrant did not specify the substance to be tested, thus by default ECHA considers that the test should be performed on the registered substance.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study using the registered substance :Long-term toxicity to sediment organisms (Annex X, 9.5.1.; test method: Sediment-water Chironomid toxicity using spiked sediment, OECD 218.

4. Sub-chronic toxicity study (90-day)

Pursuant to Article 40(3)(b) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test, but modifying the conditions under which the test is to be carried out.

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 proposed testing by the oral route. 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. The Registrant proposed testing in the rat, and ECHA considers this choice to be appropriate.

Uncertainty arises from the kidney pathology seen in the screening for reproductive/developmental toxicity study OECD 422 via oral route, and whether it does in fact arise from an alpha-2u effect. The Registrant should therefore address this concern in the OECD 408 study design. The study protocol shall be modified with additional urinalysis to characterise kidney toxicity, and additional kidney pathology to evaluate whether there is an alpha-2u mode of action. As per paragraph 30 and 32 of OECD 408, the Registrant is requested to perform urinalysis to characterise kidney toxicity, and as per paragraph 36 of OECD 408, the Registrant is requested to perform full renal histopathology including immunohistochemical determination of alpha-2u globulin, to evaluate whether there is an alpha-2u mode of action.

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

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.

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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