EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000002239-73-05/F Helsinki, 02.08.2012

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

**For Di-tert-butyl peroxide, CAS No 110-05-4 (EC No 203-733-6), 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)(e) thereof for Di-tert-butyl peroxide, CAS No 110-05-4 (EC No 203-733) submitted by [redacted] (Registrant), latest submission number [redacted], for the tonnage band of [redacted].

- Viscosity of Liquids (OECD Test Guideline 114)
- Repeated Dose 90-Day Oral Toxicity study (OECD Guideline 408) in Rodents
- Prenatal Developmental Toxicity study (OECD Guideline 414)
- Long-term toxicity testing on invertebrates (OECD Guideline 211), Daphnia magna Reproduction Test)
- Long-term toxicity testing on fish (OECD Guideline 210) Fish, Early-Life Stage Toxicity Test)
- Degradation in water and sediment. (OECD Guideline 303 A, Simulation Test - Aerobic Sewage Treatment. A: Activated Sludge Units)

On 5 November 2010, pursuant to Article 40(1) of the REACH Regulation, ECHA initiated the examination of the testing proposals set out by the Registrant in the registration dossier for the substance mentioned above.

ECHA held a third party consultation for the testing proposals from 1 July 2011 until 15 August 2011. ECHA received one comment from third parties, proposing read-across possibility from another substance for the pre-natal toxicity study. More information is provided in the section III, statement of reasons below.

On 5 January 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 3 February 2012 ECHA received comments from the Registrant, in which he proposed:

- extension of the timing for the tests
- change of the route of administration for the repeated dose 90-day study from oral to inhalation
- deletion of the OECD Guideline 309 from the original draft decision sent to the

Registrant, MSCAs and MSC.

The Registant did not update his dossier during or after the commenting phase.

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

On 3 March 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 5 March 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 not to amend the draft decision.

On 16 April 2012 ECHA referred the draft decision to the Member State Committee.

On 30 April 2012 the Registrant provided comments on the proposed amendment. The Member State Committee took the comments of the Registrant into account.

After discussion in the Member State Committee meeting on 6-8 June 2012, a unanimous agreement of the Member State Committee on the draft decision as amended by ECHA was reached on 7 June 2012 and ECHA took the decision pursuant to Article 51(6) 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 requirements of the REACH Regulation. The decision does not prevent ECHA to initiate a compliance check on the present dossier at a later stage.

## II. Testing required

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

1. Viscosity (Annex IX, 7.17., test method OECD 114 (Viscosity of liquids))
2. Sub-chronic toxicity study (90-day) in rats, inhalation route (Annex IX, 8.6.2, test method EU B.29/OECD 413)
3. Pre-natal developmental toxicity study in rats, oral route (Annex IX, 8.7.2, test method EU B.31/OECD 414)
4. Long-term toxicity testing on invertebrates (*Daphnia magna* Reproduction Test)) (Annex IX, 9.1.5, test method EU C.20/ OECD 211)
5. Long-term toxicity testing on fish, (Annex IX, 9.1.6., OECD Guideline 210 (Fish, Early-Life Stage Toxicity Test))
6. Biotic degradation (Simulation Test - Aerobic Sewage Treatment (Annex IX, 9.2.1, EU Method C.10/OECD 303A))

The Registrant shall determine the appropriate order of the studies taking into account the possible outcomes 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.

In addition, before conducting any of the tests mentioned above in points 4 and 5 the Registrant shall consult the ECHA *Guidance on information requirements and chemical safety assessment (version 1.1., May 2008)*, Chapter R7b, Section R.7.8.5 to determine the sequence in which the aquatic long-term toxicity tests are to be conducted and the necessity to conduct long-term toxicity testing on fish.

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **2 August 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 fulfil 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.

III. Statement of reasons

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

**1. Viscosity**

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

The proposed test referred to in Section II.1 above is part of the standard information requirements as laid down in Annex IX of the REACH Regulation. In addition to the proposed test, the dossier contains no data on viscosity. Accordingly, it is necessary to generate the data and to perform the test.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: viscosity in liquids (test method OECD 114) using the registered substance.

**2. Sub-chronic toxicity study (90-day)**

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

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.

In the dossier the Registrant proposed testing in rodents by the oral route. However, in his comment the Registrant proposed inhalation route in rats for the following reasons:
1. The substance is a liquid with a high vapour pressure so worker exposure via the inhalation route is likely
2. The substance caused hyperkeratosis in the forestomach of rats following repeated oral treatment indicating that the test substance can be (very) irritating. An inhalation study will give information on the potential for respiratory irritation which may be even more severe since respiratory epithelium is more vulnerable to irritants.
In this way a long-term DNEL can be set for both local and systemic effects following exposure via the most likely route to which workers are being exposed.

ECHA agrees that testing by inhalation is justifiable based on Annex IX, 8.6.2. Column 2, as inhalation is the likely route of exposure based on the properties and use pattern of the substance.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is required to carry out the proposed study: Sub-chronic toxicity study (90-day) in rats, by the inhalation route (test method: EU B.29/OECD 413) using the registered substance.

### 3. Pre-natal developmental toxicity study

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.

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 generate the data for this endpoint.

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. 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.

b) Consideration of third party information

A third Party has proposed a weight-of evidence approach for ECHA to take into account before further tests on vertebrate animals are required. As part of this approach, the third party provided results from studies tert-butyl hydroperoxide, CAS 75-91-2, by a secondary reference: OECD/SIDS, Screening Information Data Set (SIDS) of OECD High Production Volume Chemicals Programme 8 (1993) for tert-butyl hydroperoxide. In the SIDS report, oral dosage levels of 0, 5, 15 and 50 mg/kg body weight were administered to mated female rats. Neither embryotoxic nor teratogenic effects were found up to the dose of 50 mg/kg body weight.

ECHA recognises that the information as provided by the third party might be scientifically valid. Based on the received information ECHA concludes that the data is insufficient for demonstrating that the conditions of Annex XI of the REACH Regulation are met.

More specifically, ECHA could not assume that the substance has/has not a particular dangerous property because based on the available information, the toxicological profile of tert-butyl hydroperoxide is very different from the registered substance. Tert-butyl hydroperoxide is classified for acute toxicity, skin corrosion, eye damage and a skin sensitiser, as well as mutagenicity. Based on the information provided in the dossier the registered substance is classified only for mutagenicity human health endpoint.

A structural similarity could not be demonstrated because of the following: The justification provided by the third party for read-across is limited to a short note on structural similarity and reference to a SIDS document. The documentation of the applied method provided is not considered adequate to justify the read-across.

Even if the fulfilment of Annex XI requirements could not be demonstrated, ECHA acknowledges that the Registrant may himself supplement under its own responsibility the argumentation and information provided by the third party in order to make use of adaptation possibilities. This would require that the Registrant demonstrates a sufficient justification from several independent sources of information leading to the assumption/conclusion that a substance has or has not particular dangerous properties, according to the criteria laid down in Annex XI of the REACH Regulation.

c) Outcome

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, by the 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.

## 4. Long-term toxicity to aquatic invertebrates

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

The proposed test referred to in Section II.4 above is part of the standard information requirements laid down in Annex IX, 9.1.5 of the REACH Regulation and shall be proposed by the Registrant if the chemical safety assessment according to Annex I indicates the need to investigate further the effects on aquatic organisms. The Registrant has proposed a long-term toxicity test on aquatic invertebrates to refine the hazard assessment for the aquatic environment.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is thus required to carry out the proposed test: Long-term toxicity testing on invertebrates (Daphnia magna Reproduction Test) (EU Test Method C.20 / OECD 211) using the registered substance.

According to ECHA *Guidance on information requirements and chemical safety assessment*

(version 1.1., August 2008), Chapter R7b, Figure R.7.8-4 page 53, if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially more sensitive, long-term studies may be required on both. According to the integrated testing strategy, the Daphnia study is to be conducted first. If based on the results of the long-term Daphnia study and an applied assessment factor of 50 no risks are indicated, no long-term fish testing may need to be conducted.

**5. Long-term toxicity testing on fish**

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

The proposed test referred to in Section II.5 above is part of the standard information requirements laid down in Annex IX, 9.1.6 of the REACH Regulation and shall be proposed by the Registrant if the chemical safety assessment according to Annex I indicates the need to investigate further the effects on aquatic organisms. The Registrant has proposed a long-term toxicity test on fish in order to refine the hazard and risk assessment of the substance for the aquatic environment.

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 1.1., August 2008), Chapter R7b, Figure R.7.8-4 page 53, if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially more sensitive, long-term studies may be required on both. According to the integrated testing strategy, the Daphnia study is to be conducted first. If based on the results of the long-term Daphnia study and an applied assessment factor of 50 no risks are indicated, no long-term fish testing may need to be conducted.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation and taking into account the above, the Registrant is required to carry out the proposed test: Long-term toxicity testing on fish (Fish, Early-Life Stage Toxicity Test) (OECD Guideline 210) using the registered substance.

**6. Simulation Test - Aerobic Sewage Treatment**

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

The Chemical Safety Report of the registration dossier indicates that there is a risk associated with the Sewage Treatment Plant (STP). According to Annex 1 of REACH Regulation if the Risk Characterisation Ratio (RCR) indicates a risk to the Environment, then it is necessary to carry out an iterative process with amendment of one or a number of factors in the hazard or exposure assessment with the aim to demonstrate adequate control. The proposed test (EU Method C.10) can be used to refine the Predicted Environmental Concentration (PEC) and may clarify whether further simulation tests as specified under Annex 9.2.1 are required.

During the commenting period to the draft decision, the Registrant indicated that the OECD 303A would allow refinement of the PECaquatic and demonstrate that the registered substance will degrade in an STP.

As stated in the Guidance Document R7b (May 2008) page 210: "Activated Sludge Simulation Tests are not currently required under the REACH Annexes but can be used to refine the PEC and may help to determine whether either simulation tests are required or which simulation test may be the most relevant". Therefore in the context of the REACH

Regulation, Annex IX, 9.2, the proposed test is considered as a further biotic degradation test.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is thus required to carry out the proposed test: Simulation Test - Aerobic Sewage Treatment (EU Test Method C.10/OECD 303A) using the registered substance.

However, ECHA notes that the OECD 303A test cannot be used to cover the simulation biodegradation endpoint, as indicated in the Guidance on Information requirements (R7b). This Guidance (R.7.9.5.1, page 193) states that "Results from tests simulating the conditions in a sewage treatment plant (STP) (e.g. the OECD 303) cannot be used for assessing the degradation in the aquatic environment". The results from the OECD 303A test cannot be used for classification purposes (R.7.9.5.1, page 192).

The Registrant performed an Enhanced Ready Biodegradation Test (OECD 301D), which found that the substance was not readily biodegradable (6% in 98 days). The result of this enhanced ready biodegradability study would not, by itself, fulfil the information requirement of Annex IX section 9.2.1.2, but may provide the basis for adaptation of the standard information requirements provided by the REACH Regulation.

Based upon the results of the enhanced biodegradation test, the Registrant has concluded within section 8 (PBT and vPvB Assessment) of the CSR that the substance fulfils the P (persistant) criterion. ECHA considers that based on the information available in the technical dossier, the substance is potentially meeting the P or the vP criterion.

Furthermore, ECHA notes that there are two octanol-water partition coefficient (Log Kow) tests for the registered substance (Log Kow of 3.2 and 5.2) both of which have been deemed valid by the Registrant by indicating Klimisch score 1. It is also noted that a water solubility of 171 mg/L (deemed valid by the Registrant by indicating Klimisch score 1) would normally not be expected for a substance with a Log Kow value of 5.2. The Registrant has selected a log Kow of 3.2 for the registered substance based on a QSAR prediction of log Kow of 3.45. On this basis, the Registrant has concluded that the substance does not fulfil the B screening criterion.

ECHA considers that the Registrant has not sufficiently justified that the substance does not fulfil the B/vB screening criteria as laid down in Annex XIII of the REACH Regulation.

The Registrant has concluded that the substance does not fulfil the T screening criterion. ECHA notes that the substance may meet the T screening criterion on the basis of the results of the other toxicological tests required in the present decision, in due course.

Therefore, ECHA takes the view that based on the information made available in the dossier, Registrants comments and Member State Committee, there is a residual uncertainty on the PBT/vPvB assessment of the substance. Consequently, the Registrant is requested to take the above into consideration when updating the CSR.

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.

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.

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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