EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-0000004399-63-02/F Helsinki, 28 February 2014

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

For [1,3-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide, CAS No 2212-81-9 (EC No 218-664-7), 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 [1,3-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide, CAS No 2212-81-9 (EC No 218-664-7) by [redacted] (Registrant).

- *Daphnia magna* reproduction test (OECD 211);
- Sediment-Water Chironomid Toxicity Using Spiked Sediment (OECD 218);
- Repeated dose 90-day oral toxicity study (OECD 408; '*in order to better evaluate reproductive effects of repeated dose exposure, histopathology of the testes, as well as weights of reproductive organs and accessory glands will be taken (i.e. testis, epididymis, prostate, seminal vesicle). In addition sperm parameters such including sperm count, sperm morphology and sperm motility will be evaluated*'); test species not specified; and
- Developmental toxicity / teratogenicity study (OECD 414), test species and route not specified.

All tests are proposed to be performed with analogue substance [1,3(or 1,4)-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide (CAS No 25155-25-3).

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 31 October 2013, 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 present dossier at a later stage.

On 07 February 2012, 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 16 May 2012 until 02 July 2012. ECHA did receive information from third parties (see section III below).

On 31 January 2013 ECHA sent a draft decision to the Registrant.

On 14 February 2013 ECHA received comments from the Registrant. The Registrant also updated the dossier with additional arguments to justify the read across.

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

On 31 October 2013 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 did not propose amendments to the draft decision and ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

II. Testing required

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

1. Long-term toxicity testing on aquatic invertebrates (Annex IX, 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211);
2. Long-term toxicity to sediment organisms (Annex X, 9.5.1; test method: OECD 218);
3. Sub-chronic toxicity study (90-day) in rats, oral route (Annex IX, 8.6.2, test method: EU B.26/OECD 408);
   It is at the Registrant's discretion to perform the intended additional examinations during the testing program; and
4. Prenatal developmental toxicity study in rats or rabbits, oral route (Annex IX, 8.7.2, test method: EUB.31/OECD 414).

While all the originally proposed tests proposed to be carried out using the analogue substance [1,3(or 1,4)-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide are 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 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 **28 February 2016** an update of the registration dossier containing the information required by this decision.

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 shall 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 shall update his technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex IX, 9.1.6.

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 and scientific information submitted by third parties.

In relation to the testing proposals subject to the present decision, the Registrant has proposed to use a read-across approach and to perform the tests on the analogue substance [1,3(or 1,4)-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide. To the extent that all proposed testing relies upon such an identical read-across hypothesis, ECHA has considered first the validity of the proposed read-across before assessing the testing proposed (Sections 1 to 4 below).

Read-across and grouping approach

Article 13(1) of the REACH Regulation requires information on intrinsic properties of substances in particular on human toxicity to be generated whenever possible by means other than vertebrate animal tests, including from information from structurally related substances (grouping or read-across), "*provided that the conditions set out in Annex XI are met*".

ECHA emphasises that it is the Registrant's responsibility to justify and substantiate the read-across and category justification according to Annex XI, section 1.5. and to use all relevant available data.

In the present case, after receiving the draft decision the Registrant has provided additional justification to support the proposed read-across hypothesis pursuant to Annex XI, section 1.5.

Based on its assessment of the justification, ECHA concludes that the intended read-across is based on the structural similarity of the meta and the para isomers, the nearly identical physico-chemical properties of these isomers, a presumed equal chemical reactivity and the absence of effects of the target and the source substance in studies for eye and skin irritation and gene mutations in bacteria. Moreover, the Registrant points out that the meta and para isomer of a presumed breakdown product are expected to have the same toxicological profile.

ECHA cannot accept the intended read-across as it is justified by the Registrant. Structural similarity and similarity of physico-chemical properties, albeit obvious for the main constituents of source and target, are in themselves not sufficient to demonstrate that the

meta and the para isomers of the main constituents will have the same toxicological profile. The same holds for the postulated para and meta isomers of the breakdown product.

The Registrant has not substantiated why identical toxicological profiles can be expected based on the similarity in chemical structure and physicochemical properties. The discussion on the relation between structure and chemical reactivity provided by the Registrant in the dossier is too concise to suffice, primarily because it does not elaborate on the chemical reactivity of the relevant isomers to specific chemical targets in the body after exposure. It is further noted that toxicity is not only determined by direct chemical reactivity towards these chemical targets in the body, but also by other, biological interactions that may not be covered by, or predicted from, the chemical reactivity.

The Registrant further states that "*the typical impurities of the substances are not expected to have any impact on the read-across approach: indeed, the impurities of the meta isomer are contained in or very close structural analogues to those present in the mixture of the meta + para isomers.*" However, ECHA observes that, based on the analytical and compositional data, it appears the impurity levels are considerable for both substances. The differences in the type of impurities for the two substances may have a significant effect on the toxicological profiles of target and source substance, and may thus affect the possibility to read across.

Therefore, the requirements of Annex XI, section 1.5 in conjunction with Article 13(1) are not met and the read-across approach is not accepted.

Notwithstanding the rejection of the read-across by ECHA based on the information provided by the Registrant in the dossier, it is recognized that the source substance consist for a large part ([redacted]) of the main constituent (the meta isomer) of the target substance. ECHA notes that by testing the source substance and applying a worst-case approach or relevant assessment factors for mixture testing, it is conceivable that the Registrant could construct a weight of evidence case for the target substance, in accordance with Annex XI, Section 1.2. In the dossier, the Registrant did, however, not follow this approach.

1. Long-term toxicity to aquatic organisms

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X and XI.

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 (unless already provided as part of Annex VII 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 has submitted a testing proposal for *Daphnia magna* reproduction test (OECD 211) to cover this endpoint. The Registrant has suggested using a reportedly analogue substance [1,3(or 1,4)-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide for the test.

The Registrant provided the following justification for conducting the proposed test: *'According to claimed uses of the substance, aquatic compartment exposure is likely. At the moment no data is available for characterizing 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.'*

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.

Since the Registrant has not justified why this information requirement can be fulfilled by conducting the proposed test on a reportedly analogue substance [1,3(or 1,4)-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide, the test on this analogue substance must be rejected. Instead, the test has to be carried out using the registered substance.

Therefore, pursuant to Article 40(3)(c) 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, while the originally proposed test on the analogue substance [1,3(or 1,4)-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide (CAS No 25155-25-3) is rejected in accordance with Article 40(3)(d) of the REACH Regulation.

2. Long-term toxicity to sediment organisms

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X and XI.

Long-term toxicity to sediment organisms is a standard information requirement as laid down in Annex X, section 9.5.1. of the REACH Regulation. Column 2 of Annex X, 9.5.1. specifies that long-term toxicity testing shall be proposed by the registrant if the results of the chemical safety assessment according to Annex I indicates the need to investigate further the effects of the substance and/or degradation products on sediment organisms. The information on this endpoint is not available in the technical dossier for the registered substance and is not a standard information requirement for this tonnage band.

The Registrant has proposed a sediment-water Chironomid toxicity test using spiked sediment (OECD 218). The Registrant has suggested using a reportedly analogue substance [1,3(or 1,4)-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide for the test.

ECHA notes that in proposing the test it is apparent that the Registrant considered that there is a need to perform long-term toxicity testing on sediment organisms. ECHA has examined this testing proposal considering all the relevant information available in the technical dossier. The substance is adsorptive 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.

Since the Registrant has not justified why this information requirement can be fulfilled by conducting the proposed test on a reportedly analogue substance [1,3(or 1,4)-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide, the test on this analogue substance must be rejected. Instead, the test has to be carried out using the registered substance.

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is required to carry out the proposed study: Long-term toxicity to sediment organisms (Annex X, 9.5.1, test method: OECD 218) using the registered substance, while the originally proposed test on the analogue substance [1,3(or 1,4)-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide (CAS No 25155-25-3) is rejected in accordance with Article 40(3)(d) of the REACH Regulation.

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

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X and XI.

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 proposed a repeated dose 90-day oral toxicity study (OECD 408) by the oral route using a reportedly analogue substance[1,3(or 1,4)-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide .

In the light of the physical-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.

Since the Registrant has not justified why the present information requirement can be fulfilled by conducting the proposed test on the above analogue substance, the test on the analogue substance must be rejected. Instead, the test has to be carried out using the registered substance.

ECHA notes that the Registrant has not specified the species to be tested. According to the test method EU B.26/OECD 408 the rat is the preferred rodent species. ECHA considers this species as being appropriate.

Moreover, the Registrant has proposed to extend the sub-chronic toxicity study (90-day) by including additional examinations/parameters as follows: *"in order to better evaluate reproductive effects of repeated dose exposure, histopathology of the testes, as well as weights of reproductive organs and accessory glands will be taken (i.e. testis, epididymis, prostate, seminal vesicle). In addition sperm parameters such including sperm count, sperm morphology and sperm motility will be evaluated'.*

ECHA points out 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 fulfil the standard information requirements in the registration dossier for reproductive toxicity at the next tonnage level (at 1 000 tonnes or more per year) set out in Annex X, 8.7.3. unless Annex X, 8.7. column 2 adaptation can be applied.

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, while the originally proposed test on the analogue substance [1,3(or 1,4)-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide (CAS No 25155-25-3) is rejected in accordance with Article 40(3)(d) of the REACH Regulation.

4. Pre-natal developmental toxicity study

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X and XI.

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 proposed a developmental toxicity / teratogenicity study (OECD 414) using a reportedly analogue substance [1,3(or 1,4)-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide to cover the present endpoint.

While the information gap exits, ECHA notes that the Registrant has not justified why it can be fulfilled by conducting the proposed test on the above analogue substance. Accordingly, the test on the analogue substance must be rejected and the test has to be carried out using the registered substance.

The Registrant has not specified 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 that these default parameters appropriate and testing should be performed by the oral route with the rat or rabbit 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 while the originally proposed test on the analogue substance [1,3(or 1,4)-phenylenebis(1-methylethylidene)]bis[tert-butyl] peroxide (CAS No 25155-25-3) is rejected in accordance with Article 40(3)(d) of the REACH Regulation.

IV. Adequate identification of the composition of the tested material

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. If the registration of the substance covers different grades, the sample used for the new studies must be suitable to assess these.

Furthermore, 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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