ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-2114323788-39-01/F Helsinki, 30 March 2016

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

For 1,1,3,3-tetramethylbutyl hydroperoxide, CAS No 5809-08-5 (EC No 227-369-2), 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 1,1,3,3-tetramethylbutyl hydroperoxide, CAS No 5809-08-5 (EC No 227-369-2), submitted by [redacted] (Registrant).

- Viscosity of Liquids (OECD 114).
- Repeated Dose 90-Day Oral Toxicity in Rodents (OECD 408), with additional histopathological examination of the reproductive organs and immunohistochemical staining of the kidneys of male animals.
- Prenatal Developmental Toxicity Study (OECD 414) in rats via oral administration.
- Simulation Test - Aerobic Sewage Treatment. A: Activated Sludge Units (OECD 303A).
- *Daphnia magna* Reproduction Test (OECD 211).

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 the deadline for updating (12 March 2015) communicated to the Registrant by ECHA on 3 February 2015.

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 registration dossier containing the above-mentioned testing proposals for further examination pursuant to Article 40(1) on 2 April 2013.

ECHA held a third party consultation for the testing proposals from 15 July 2014 until 29 August 2014. ECHA did not receive information from third parties.

On 11 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. That draft decision was based on submission number [redacted]

On 8 December 2014 ECHA received comments from the Registrant on the draft decision twice.

On 8 December 2014 the Registrant updated his registration dossier twice. The latter update was submitted with submission number [redacted]

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

On 23 July 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. Subsequently, proposal(s) for amendment to the draft decision were submitted.

On 28 August 2015 ECHA notified the Registrant of the proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposals for amendment within 30 days of the receipt of the notification. The ECHA Secretariat reviewed the proposals for amendment received and amended the draft decision.

On 7 September 2015 ECHA referred the draft decision to the Member State Committee.

By 28 September 2015, in accordance to Article 51(5), the Registrant provided comments on the proposals for amendment. In addition, the Registrant provided comments on the draft decision. The Member State Committee took the comments on the proposals for amendment of the Registrant into account. The Member State Committee did not take into account the Registrant's comments on the draft decision as they were not related to the proposals for amendment made and are therefore considered outside the scope of Article 51(5).

After discussion in the Member State Committee meeting on 27-29 October 2015, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 27 October 2015.

ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Testing required

A. Tests required pursuant to Article 40(3)

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

1. Viscosity (Annex IX, Section 7.17.; test method OECD 114);
2. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26/OECD 408) in rats, including 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 examinations during the testing program;
3. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31/OECD 414) in rats or rabbits, oral route;

4. Biotic degradation (Simulation Test - Aerobic Sewage Treatment (Annex IX, 9.2.1, test method: EU C.10/OECD 303A));
5. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211);

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

6. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: Fish, Acute Toxicity Test, OECD 203);
7. Fish, early-life stage (FELS) toxicity test (Annex IX, Section 9.1.6.1.; test method: Fish, early-life stage toxicity test, OECD 210).

The sequence for information requests 5, 6 and 7 above is further outlined in section III of this decision.

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 requests in this decision, or to fulfil otherwise the information requirements 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 **8 October 2018** 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.

A. Tests required pursuant to Article 40(3)

1. Viscosity (Annex IX, Section 7.17.)

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

"Viscosity" is a standard information requirement as laid down in Annex IX, Section 7.17. of the REACH Regulation. The information on this endpoint is not available for the registered substance subject to the present decision 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 study Viscosity of Liquids (OECD 114). ECHA notes that at the temperature of 20 °C, the registered substance is a liquid.

ECHA considers the proposed test appropriate and testing should be performed with the registered substance.

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

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

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 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) "*with additional histopathological examination of the reproductive organs and immunohistochemical staining of the kidneys of male animals.*"

ECHA agrees that the oral route is the most appropriate route of administration for testing.

The registered substance is a liquid at ambient temperature. The vapour pressure of the substance is indicated to be 15 Pa at 20°C; therefore, exposure to vapour is regarded as not likely.

In its official comments to the draft decision, the Registrant indicated its intention to update the dossier with regard to the covered uses. In the original draft decision sent to the Registrant, ECHA changed the proposed oral route to inhalation because uses with spray application were included in the registration and human inhalation exposure to aerosols was indicated.

In his registration dossier update (submission number [redacted]) the registrant explained the absence of process catergories (PROCs) that would lead to aerosol exposure by the inhalation route. ECHA secretariat agrees with the Registrant there are no process categories within the exposure scenario that lead to significant release of aerosol of the registeresd substance. Consequently, administration by the oral route is most appropriate.

The Registrant did not specify the species to be used for testing. According to the test method 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 *"immunohistochemical staining of the kidneys of male animals".* ECHA notes that in the 28-day repeated dose toxicity study in rats hyaline droplets were noted in the kidneys of male animals at 100 mg/kg/day. The fact that these effects were only observed in male rats indicates that the registered substance may induce alpha-2u-globin-mediated nephropathy. Since humans do not excrete alpha-2u-globin, this mode of action is not relevant to humans. For this reason, ECHA agrees with the registrant to include 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) with immunohistochemical investigation of renal pathology to determine if the pathology is indeed mediated by alpha-2u globulin.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is requested to carry out the following study 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) including urinalysis and a full histopathological examination with immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy.

Notes for consideration by the Registrant

The Registrant proposed to extend the sub-chronic toxicity study (90 day) by including "*additional histopathological examination of the reproductive organs*". 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, if the condition of Annex IX, Section 8.7.3., Column 1 is fulfilled, the proposed extension of the study presently requested does not fulfil the standard information requirement in the registration dossier for reproductive toxicity set out in Annex IX, Section 8.7.3.

3. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

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 proposed testing by the oral route. 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 the default parameters of the test guideline are appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

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).

4. Biotic degradation (Simulation Test - Aerobic Sewage Treatment (Annex IX, 9.2.1, Test Method: EU C.10/OECD 303A))

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

The Registrant, in the registration dossier update (submission number [redacted]) in Section 5.2.2 of IUCLID, stated that: "*The necessity of further investigations into the environmental fate of 1,1,3,3-tetramethylbutyl hydroperoxide is considered limited in view of its low potential to bioaccumulate and limited environmental exposure. (...) Releases of 1,1,3,3-tetramethylbutyl hydroperoxide is only expected at production sites of the peroxide and polymer production sites using the organic peroxide as initiator. (...) Aqueous effluents are either incinerated or treated in biological wastewater treatment systems. 1,1,3,3-Tetramethylbutyl hydroperoxide is expected to be reduced completely in biological wastewater treatment. Exposure of the water compartment to 1,1,3,3-tetramethylbutyl hydroperoxide is therefore highly unlikely.*"

ECHA notes that the Registrant has stated that the exposure of the water compartment is in this specific scenario highly unlikely and therefore, it is expected that surface water exposure and risk are very limited. As stated in the Guidance Document R7b (November 2014) page 229: "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 an appropriate 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.

Notes for consideration by the Registrant

The Registrant performed a Ready Biodegradability: Closed Bottle Test (OECD 301D), which found that the registered substance was not readily biodegradable (0% in 60 days). Based upon the results of the screening biodegradation test, the Registrant has concluded that the registered substance fulfils the vP (and P) (very persistant and persistant) criterion. Besides, the Registrant indicates that the substance has a low bioaccumulation potential (log Kow 2.9). Thus, the substance will not be either a PBT or vPvB substance. However, the Registrant has not provided PBT or vPvB properties of 2-hydroxy-2,4,4-trimethylpentane, the only indicated degradation product.

According to the guidance document on suitability for PBT/vPvB assessment (R.7.9.5.2, page 213), "Where a substance is degraded by abiotic means or partly biodegraded it may be necessary to consider whether there are any breakdown products or metabolites that are formed that could be potential PBTs/vPvBs. Where the original substance forms a breakdown product or metabolite that could be a PBT/vPvB, there will need to be an assessment of how much the breakdown product or metabolite constitutes compared with the parent substance". Therefore, the PBT/vPvB properties of the degradation products at some stage need to be addressed.

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 210) 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*". According to the guidance document, the OECD 303 studies are not included in the relevant tests to assess persistence in the environment (R.7.9.5.2, page 198).

Also regarding classification of the registered substance, the results from the OECD 303A test cannot be used for classification purposes (R.7.9.5.1, page 196).
In accordance with Annex IX 9.2.1, Annex I Sections 4, 5 and 6 of the REACH Regulation the Registrant should revise the PBT, Exposure and Risk Characterisation Ratio assessments when results of the test detailed above are available. If a relevant risk to receiving waters would still be indicated at the updated CSA and/or if the registered substance major degradants are PBT/vPvB, a new simulation testing proposal should be submitted as a further refinement. The Registrant is also advised to consult the ECHA Guidance on information requirements and chemical safety assessment (version 2.0, November 2014), Chapter R.11.1.3. and Figure R. 11-1 on PBT assessment for the integrated testing strategy for persistency assessment in particular taking into account the degradation products of the registered substance.

5. 6. and 7. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.), Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.), and Fish, early-life stage (FELS) toxicity test (Annex IX, Section 9.1.6.1.)

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test, i.e. long-term toxicity testing on aquatic invertebrates. In addition, pursuant to Article 40(3)(c) of the REACH Regulation, ECHA may require the Registrant to carry out one or more additional tests in case of non-compliance of the testing proposal with Annexes IX, X or XI of the REACH Regulation.

"Short-term toxicity testing on fish", "Long-term toxicity testing on aquatic invertebrates" and "Long-term toxicity testing on fish" are standard information requirements as laid down in Annex VIII, Section 9.1.3. and Annex IX, Sections 9.1.5. and 9.1.6. of the REACH Regulation respectively.

The Registrant has submitted a testing proposal for testing the registered substance for long-term toxicity testing on aquatic invertebrates *Daphnia magna* reproduction test, EU C.20/OECD 211. ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 9.1.5 of the REACH Regulation, only.

Regarding the standard information requirements for Annex VIII, Section 9.1.3. and Annex IX, Sections 9.1.6. of the REACH Regulation respectively, the Registrant has provided the following justification in Section 6.1.1 and Section 6.1.2. of the technical dossier in the form of a word document entitled : "*Based on the Organic Peroxides consortium's position paper "Adaption of the Assessment Factor for Aquatic PNEC Derivation for Organic Peroxides - Low acute to chronic ratio" (author: CEHTRA, Report no. CFR-12.012), see also attachment in IUCLID section 13) fish are generally considered the least sensitive of the 3 trophic levels. For animal welfare purposes, a fish test is waived. and also that it will add no extra value to the risk assessment process".* This document addresses the acute to chronic ratio of peroxides and there are several toxicity data for fish, *Daphnia* and algae for other peroxides given.

ECHA notes that the justification for waiving provided by the Registrant does not meet the criteria of either the specific adaptation rules of Column 2 of Annex VIII, section 9.1.3. or Column 2 of Annex IX, section 9.1.6. or of the general adaptation rules of Annex XI.

The justification of the Registrant does not meet the criteria due to the following reasons:

- In the registration dossier submission on which this decision is based, a justification of the read-across adaptation or weight of evidence, and other adequate and reliable documentation was not provided. It is not clarified to which extent the data on structurally different organic peroxides are relevant for the registered substance.
- The "Adaption of the Assessment Factor for Aquatic PNEC Derivation for Organic Peroxides - Low acute to chronic ratio" does not show fish to be substantially more sensitive than Daphnia or algae (i.e. by factor of 10 or more).

ECHA notes that no information on short or long-term toxicity to fish is available in the registration dossier. In the absence of information on short-term toxicity to fish, it cannot be concluded if fish or invertebrates or algae/aquatic plants are shown to be substantially more sensitive.

The Registrant's justification does not fulfil the standard information requirement of Annex VIII, Section 9.1.3. or Annex IX, Sections 9.1.6. of the REACH Regulation. Therefore there is a data gap for both short- and long-term fish toxicity.

In the context of a testing proposal examination and in order to ensure use of the integrated testing strategy, the short-term toxicity study testing on fish is to be conducted first. If based on the results, either fish or aquatic invertebrates are shown to be substantially more sensitive than the respective other species, according to ECHA *Guidance on information requirements and chemical safety assessment* (version 2.0, November 2014), Chapter R7b (Section R.7.8.5 including Figure R.7.8-4), a long-term study on the more sensitive species is required, i.e. either on invertebrates or fish. On the contrary, 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. In such a case, according to the integrated testing strategy, the invertebrate (*Daphnia* preferred) study is to be conducted first. If based on the results of the long-term invertebrate study and the application of a relevant assessment factor no risks are observed (PEC/PNEC<1), no long-term fish testing may need to be conducted. However, if a risk is indicated, then also long-term fish testing may need to be conducted.

In view of the possibility that all three studies, short term fish, long term daphnia and long term fish, need to be conducted in sequence, the initial deadline proposed in the draft decision that was 24 months has been prolonged to 30 months.

ECHA considers that for the endpoint of long-term toxicity testing on fish pursuant to Annex IX, section 9.1.6., the FELS toxicity test according to OECD 210 is the most sensitive of the standard fish tests available as it covers several life stages of the fish from the newly fertilised egg, through hatch to early stages of growth and should therefore be used (see ECHA *Guidance on information requirements and chemical safety assessment* (version 2.0, November 2014), Chapter R7b, Figure R.7.8-4 page 26). The test method OECD 210 is also the only suitable test currently available for examining the potential toxic effects of bioaccumulation (ECHA Guidance R7b, version 2.0, November 2014, p. 26). For these reasons, ECHA considers the FELS toxicity test using the test method OECD 210 as appropriate and suitable.

Therefore, pursuant to Article 40(3)(a) and (c) of the REACH Regulation, the Registrant is required to carry out the following studies using the registered substance subject to the present decision: Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: Fish, Acute Toxicity Test, OECD 203) and, based on the results of that test: Long-term toxicity testing on aquatic invertebrates (Annex IX, 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211) and/or Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.; test method: Fish, early-life stage toxicity test, OECD 210).

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. The Registrant must note, however, that this information has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

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

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.

Authorised[1] by Claudio Carlon, Head of Unit, Evaluation E2

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.