ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 10 December 2018

Addressee: [redacted]

Decision number: TPE-D-2114453451-55-01/F
Substance name: Dihexadecyl peroxodicarbonate
EC number: 247-611-0
CAS number: 26322-14-5
Registration number: [redacted]
Submission number: [redacted]
Submission date: 15/02/2018
Registered tonnage band: 100-1000

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation ((EC) No 1907/2006) (the REACH Regulation), ECHA examined your testing proposal(s) and decided as follows.

Your testing proposals are accepted and you are requested to carry out:

1. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats using the analogue substance ditetradecyl peroxydicarbonate, CAS No 53220-22-7, EC No 258-436-4.**
2. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rat or rabbit), oral route using the analogue substance ditetradecyl peroxydicarbonate, CAS No 53220-22-7, EC No 258-436-4.**

You have to submit the requested information in an updated registration dossier by **17 December 2020**. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons for this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] by Kevin Pollard, Head of Unit, Evaluation, E1

[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.

Appendix 1: Reasons

The decision of ECHA is based on the examination of the testing proposals submitted by you and scientific information submitted by third parties.

You have proposed to cover the human health information requirements for a sub-chronic toxicity study (Annex IX, Section 8.6.2.) and a pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) by applying a read-across approach whereby these studies would be conducted with the analogue substance ditetradecyl peroxydicarbonate (CAS No 53220-22-7, EC No 258-436-4; hereafter referred to as "source substance") and then read-across to the substance subject to this decision (hereafter referred to as "target substance"), in accordance with the principles set out in Annex XI, Section 1.5.

ECHA has considered first the scientific validity of the read-across hypothesis (see below preliminary considerations: "Grouping and read-across"), before assessing the testing proposed (see Sections 1. and 2. below).

Grouping and read-across

Legal Background on ECHA's assessment of the grouping of substances and read-across hypothesis

The evaluation by ECHA of testing proposals submitted by registrants aims at ensuring that generation of information is tailored to real information needs. To this end, it is necessary to consider whether programmes of testing proposed by you are appropriate to fulfil the relevant information requirements and to guarantee the identification of health and environmental hazards of substances. In that respect, the REACH Regulation aims at promoting wherever possible the use of alternative means, where equivalent results to the prescribed test are provided on health and environmental hazards.

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

The first Recital and the first Article of the REACH Regulation establish the "promotion of alternative methods for assessment of hazards of substances" as an objective pursued by the Regulation. In accordance with that objective, ECHA considers whether a prediction of the relevant properties of the substance subject to the present decision by using the results of the proposed tests is plausible based on the information currently available.

According to Annex XI, Section 1.5. there needs to be structural similarity among the substances within a group or a category and furthermore, it is required that the relevant properties of a substance within the group can be predicted from the data for reference substance(s) by interpolation, and the data should be adequate for the purpose of classification and labelling and/or risk assessment. Furthermore, Annex XI, Section 1.5 lists several additional requirements, including that adequate and reliable documentation of the applied method is to be provided.

Description of the proposed grouping and read-across approach and information submitted

Your read-across hypothesis is based on similarities in the chemical structures and in the physico-chemical and toxicological properties between the source substance and the target substance. You state that: "*The hypothesis is that as a result of structural similarity, the different compounds cause the same type of effects (Scenario 2; RAAF, 2017). The predicted strength of the effects may be similar or based on a worst case. The analogue approach for the read-across uses their physico-chemical properties, available (eco)toxicological data, and some support from QSAR predictions where needed.*"

You indicated that "*The target substance (DCPDC) is comprised of a long aliphatic hydrocarbon chain linked to a peroxydicarbonate group. For read across purposes reference is made to a suitable congener of the family of long-chain aliphatic peroxydicarbonates. The chosen read across substance shares the same functional groups with the test substance. More specifically, the peroxydicarbonate DMPDC with comparable aliphatic tail length was found to be a suitable candidate for the read across.*" "*The molecular formula of Dicetylperoxydicarbonate (DCPDC) and Dimyristiylperoxydicarbonate (DMPDC) are very closely related and they differ only by an ethyl group on each side of the peroxide bridge. Both substances are long-chain aliphatic peroxydicarbonates.*"

You compared the hazards of the main impurities of the target substance ([redacted]) and the source substance ([redacted]) and you concluded "*these substances show no systemic effects and have very similar physicochemical and (eco)toxicological properties they are not expected to influence the toxicological properties of the target or source chemicals, and hence not expected to have an impact on the read across approach*".

You further concluded that the physico-chemical are very similar, e.g., both substances are readily biodegradable and the vapour pressure of both substances is very low.

You further indicated that the target and source substances have similar degradation products. After thermal degradation the target substance breaks down to [redacted] and the source substance to [redacted]. [redacted] are the main degradation products also in aqueous solution at 37°C pH 1.2. You provided information showing that these breakdown products have a very similar physicochemical profile and are non-hazardous.

With respect to the toxicity profile of target and source substance, you demonstrated a similar toxicological profile. More specifically, you compared the information on acute toxicity, eye and skin irritation, sensitisation and genotoxicity for target and source substance and demonstrated their similarity in your read-across justification document. Furthermore, you provided study reports for OECD TG 422 screening studies for the target and the source substance, both showing no toxicity up to 1000 mg/kg bw/d.

ECHA analysis of the grouping approach and read-across hypothesis in light of the requirements of Annex XI, 1.5.

According to the provisions of Annex XI, Section 1.5. of the REACH Regulation, application of the grouping and read-across concept requires that the properties of a substance may be predicted from data on another structurally similar substance.

ECHA has analysed the provided information and concluded that you have provided sufficient information to demonstrate similarity of target and source substance.

ECHA concludes that the read-across hypothesis can be considered plausible as the underlying toxicological information is complete and relevant and supports the hypothesis, and you may be able to predict the relevant properties of the substance subject to the present decision by using the results of the proposed tests on the read-across substance. Therefore, the result of the proposed tests can be considered adequate for the purpose of classification and labelling and/or risk assessment. Hence, ECHA concludes that the criteria of Annex XI, Section 1.5. are met.

1. 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.

You have submitted a testing proposal for a sub-chronic toxicity study (90 day) in rats by the oral route according to OECD TG 408 with the analogue substance ditetradecyl peroxydicarbonate (CAS No 53220-22-7, EC No 258-436-4; pure substance (hypothetical test material)).

ECHA requested your considerations for alternative methods to fulfil the information requirement for Sub-chronic toxicity (90-day): oral. ECHA notes that you provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

ECHA has evaluated your proposal to perform the test with the analogue substance ditetradecyl peroxydicarbonate (EC No 258-436-4). For the reasons outlined above (see "Grouping and read-across"), ECHA considers the proposed read-across approach plausible.

Furthermore, you indicated that the test will be performed with the pure analogue substance indicated as "hypothetical test material". ECHA notes that the composition of the analogue substance has been reported to contain (1) ditetradecyl peroxydicarbonate (EC No 258-436-4) with typical concentration of [redacted] and (2) [redacted] with the typical concentration of [redacted], as an impurity. It is your responsibility to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the registered substance as described in the registration dossier (see Appendix 3).

You proposed testing by the oral route. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA agrees that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, even though the information indicates

that human exposure to the registered substance by the inhalation route is likely, there is no concern for severe local effects following inhalation exposure. Hence, the test shall be performed by the oral route using the test method OECD TG 408.

Therefore, ECHA considers that the proposed study performed by the oral route with the analogue substance ditetradecyl peroxydicarbonate (CAS No 53220-22-7, EC No 258-436-4) is appropriate to fulfil the information requirement of Annex IX, Section 8.6.2. of the REACH Regulation.

You proposed testing in rats. According to the test method OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties might partially be sufficient to fulfil this information requirement.

A third party has indicated following:

"*The substance is essentially insoluble in water, is of relatively high molecular weight and is not predicted to be bioavailable (Lipinski Rules; OASIS). The substance is not classified for health effects. Available data report very low toxicity; the acute oral LD50 is >2000 mg/kg bw and the NOAEL for an OECD 422 screening study is 1000 mg/kg bw/d. The substance is not classified for human health endpoints and therefore meets the definition of a low (sub)acute toxicity profile according to Taylor et al (2014), Taylor & Andrew (2017). Given the low toxicity of the substance and the likely low bioavailability, the value of the proposed 90-day study is therefore questioned. The hydrolysis study presented in the Registration Dossier indicates the possibility of some hydrolysis of the substance to form cetyl (C16) alcohol, which may be orally bioavailable. However there would appear to be adequate data in the Registration Dossier for this substance to address the repeated dose toxicity; therefore read-across to the hydrolysis product may also be possible. The Registrant proposes that the 90-day study is performed with a read-across substance (the C14 structural analogue). While this proposed read-across is scientifically justified, arguments relating to low toxicity and bioavailability equally apply to this substance. Taylor K et al (2014). The added value of the 90-day repeated dose oral toxicity test for industrial chemicals with a low (sub)acute toxicity profile in a high quality dataset. Regul Toxicol Pharmacol. 69(3):320-332. Taylor K & Andrew DJ (2017). The added value of the 90-day repeated dose oral toxicity test for industrial chemicals with a low (sub)acute toxicity profile in a high quality dataset: An update. Regul Toxicol Pharmacol. 90:258-261.*"

ECHA notes that, as explained above, read-across to the analogue substance ditetradecyl peroxydicarbonate (EC No 258-436-4) as proposed and adequately documented is plausible. Therefore, the 90-day subchronic toxicity study should not be performed with the registered substance but with the analogue substance.

With respect to the added value of a 90-day repeated dose oral toxicity study for industrial chemicals with a low (sub)acute toxicity profile, ECHA notes that it is the registrant's responsibility to consider and justify in the registration dossier any adaptation of the information requirements in accordance with Annex IX, Section 8.6.2., column 2, fourth indent. This adaptation specifies that a sub-chronic toxicity study (90-day) does not need to be conducted if "*the substance is unreactive, insoluble and not inhalable and there is no evidence of absorption and no evidence of toxicity in a 28-day study, particularly if such a*

pattern is coupled with limited human exposure". ECHA notes that all criteria need to be met.

In your comments following the procedure set out in Article 50(1) of the REACH Regulation you have indicated your agreement to provide this information.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study with the analogue substance ditetradecyl peroxydicarbonate (CAS No 53220-22-7, EC No 258-436-4): Sub-chronic toxicity study (90-day) in rats, oral route (test method: OECD TG 408).

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

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.

You have submitted a testing proposal for a pre-natal developmental toxicity study in rats according to OECD TG 414 by the oral with the analogue substance, ditetradecyl peroxydicarbonate (CAS No 53220-22-7, EC No 258-436-4; pure substance (hypothetical test material)).

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity (pre-natal developmental toxicity). ECHA notes that you provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

ECHA has evaluated your proposal to perform the test with the analogue substance, ditetradecyl peroxydicarbonate (EC No 258-436-4). For the reasons outlined above (see "Grouping and read-across"), ECHA considers the proposed read-across approach plausible. Furthermore, you indicated that the test will be performed with the pure analogue substance indicated as "hypothetical test material". ECHA notes that the composition of the analogue substance has been reported to contain (1) ditetradecyl peroxydicarbonate (EC No 258-436-4) with typical concentration of [redacted], and (2) [redacted] with the typical concentration of [redacted], as an impurity.

It is your responsibility to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the registered substance as described in the registration dossier (see Appendix 3).

ECHA considers that the proposed study performed with the analogue substance ditetradecyl peroxydicarbonate (CAS No 53220-22-7, EC No 258-436-4) is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

You proposed testing with the rat as a first species. According to the test method TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with the rat or rabbit as a first species.

You proposed testing by the oral route. ECHA agrees that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

In your comments following the procedure set out in Article 50(1) of the REACH Regulation you have indicated your agreement to provide this information.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed study with the analogue substance ditetradecyl peroxydicarbonate (CAS No 53220-22-7, EC No 258-436-4): Pre-natal developmental toxicity study in a first species (rats or rabbits), oral route (test method: OECD TG 414).

Notes for your consideration

For the selection of the appropriate species you are advised to consult ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017), Chapter R.7a, Section R.7.6.2.3.2.

Appendix 2: Procedural history

ECHA received your registration containing the testing proposals for examination in accordance with Article 40(1) on 15 February 2018.

ECHA held a third party consultation for the testing proposals from 23 April 2018 until 7 June 2018. ECHA received information from third parties (see Appendix 1).

This decision does not take into account any updates after **28 September 2018**, 30 calendar days after the end of the commenting period.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA notified you of the draft decision and invited you to provide comments.

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request(s).

Regarding your comment on the deadline of the draft decisions, ECHA notes there was no registrant's comment from the analogue substance ditetradecyl peroxydicarbonate, CAS No 53220-22-7, EC No 258-436-4 testing proposal draft decision to extend the deadline to >24 months, but to extend it to 24 months. All related draft decisions (CCH & TPE) deadlines are set at 24 months.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided in your 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.

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of the Member States.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests 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 or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests 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 tests to be assessed.

4. If the required tests are conducted with an analogue substance in the context of a read-across approach, the identity of the test material used to perform the test should be specified in line with the ECHA's Practical Guide on "How to use alternatives to animal testing to fulfil your information requirements" (chapter 4.4). This is required to show that the test material is representative of the analogue substance identified in the read-across approach and used to predict the properties of the registered substance.