Decision number: TPE-D-2114328778-35-01/F Helsinki, 26 April 2016

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

**For sodium O,O-diethyl dithiophosphate, EC No 222-079-2 (CAS No 3338-24-7), 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 sodium O,O-diethyl dithiophosphate, EC No 222-079-2 (CAS No 3338-24-7), submitted by [redacted] (Registrant).

- 90-day oral toxicity study (OECD 408) in rodents, oral route using the analogue substance sodium O,O-diisobutyl dithiophosphate (EC No 258-508-5);
- Developmental toxicity/teratogenicity study (OECD 414) in rats, oral route using the analogue substance sodium O,O-diisobutyl dithiophosphate (EC No 258-508-5).

This decision is based on the registration as submitted with submission number [redacted], for the tonnage band of [redacted] tonnes per year. This decision does not take into account any updates after 6 June 2015 i.e. 30 calendar days after the end of the commenting period.

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 4 June 2014.

ECHA held a third party consultation for the testing proposals from 18 September 2014 until 3 November 2014. ECHA did not receive information from third parties.

On 30 March 2015 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 the registration dossier as updated by submission number [redacted].

On 14 April 2015 ECHA received comments from the Registrant on the draft decision. On 4 June 2015 the Registrant updated his registration by submission number [redacted]. The ECHA Secretariat considered the Registrant's comments and update. The information is reflected in the Statement of Reasons (Section III) whereas no amendments to the Information Required (Section II) were made.

On 3 March 2016 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.

As no proposal for amendment was submitted, ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

## II. Testing required

### A. Tests required pursuant to Article 40(3)

The Registrant shall carry out the following 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:

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26/OECD 408) in rats;
2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31/OECD 414) in rats or rabbits, oral route.

While the originally proposed tests for a 90-day oral toxicity study (OECD 408) and developmental toxicity/teratogenicity study (OECD 414) proposed to be carried out using the analogue substance sodium O,O-diisobutyl dithiophosphate (EC No 258-508-5) are rejected pursuant to Article 40(3)(d) of the REACH Regulation.

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 **03 May 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.

ECHA
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## III. Statement of reasons

### A. Tests required pursuant to Article 40(3)

#### 0. Read-across approach

The decision of ECHA is based on the examination of the testing proposals submitted by the Registrant for the registered substance proposed to be performed with the analogue substance sodium O,O-diisobutyl dithiophosphate (EC No 258-508-5) and the submitted read-across justification. ECHA has considered first the scientific validity of the read-across hypothesis before assessing the testing proposed (sections III.1. and III.2.).

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "*provided that the conditions set out in Annex XI are met*".
According to Annex XI, 1.5. there needs to be structural similarity among the substances within a group or category and furthermore, it is required that the relevant properties of a substance within the group can be predicted from the data for the reference substance(s) by interpolation, and the data should be adequate for the purpose of classification and labelling and/or risk assessment. The following analysis presents the Registrant's justification for the proposed read-across approach and hypothesis, together with ECHA's analysis concerning the read-across justification in both a generic and an endpoint-specific context.

The Registrant intended to cover the human health information requirements for a sub-chronic toxicity (90-day) study (Annex IX, 8.6.2.) and pre-natal developmental toxicity study (Annex IX, 8.7.2.) by applying a read-across approach in accordance with the principles set out in Annex XI, Section 1.5. According to the Registrant, the read-across hypothesis is based on similarities in the chemical structures and in the physico-chemical properties between the target substance, sodium O,O-diethyl dithiophosphate, EC No 222-079-2(CAS No 3338-24-7) and the analogue substance, sodium O,O-diisobutyl dithiophosphate (EC No 258-508-5) as source substance. The Registrant states that "*the very similar structure of the two substances gives rise to a great overlap in physico-chemical properties significant for environmental and toxicochemical assessment*", therefore he considers that "*based on the structural similarities, the read-across approach is supported*". The Registrant concludes that "*based on the limited differences between the source and target substances chemical structures, and the overlap of physical/chemical properties, no major difference in repeated dose toxicity is to be expected*".

To support the read-across hypothesis, the Registrant has included a read-across justification document in which he addresses and compares the chemical structure and physico-chemical properties of the registered substance, sodium O,O-diethyl dithiophosphate, EC No 222-079-2(CAS No 3338-24-7) and the analogue substance, sodium O,O-diisobutyl dithiophosphate (EC No 258-508-5). Based on this document and the information therein contained, the Registrant concludes that the two substances are very similar in chemical structure and in the physico-chemical properties. Additionally, the Registrant provides consideration on the toxicokinetic properties of both substances based on the physico-chemical properties of the substances in the absence of toxicokinetic experimental data, and concludes that: "*absorption and bioaccumulation of the chemicals is not expected.*" Finally, the Registrant provides a data matrix presenting the existing toxicity data for both substances, including the available toxicity data of the registered (i.e. the target) and the source substance.

The Registrant considers that due to the great overlap in physico-chemical properties, no major differences are expected in relation to repeated dose toxicity, thus validating the read-across approach.

ECHA has analysed the information and documentation provided in the registration dossier in light of the requirements of Annex XI, Section 1.5 of the REACH Regulation and concludes that the requirements of Annex XI, Section 1.5 are not met for the reasons below.
ECHA notes that the Registrant outlines similarities in the chemical structures between the source and target substances. ECHA considers that similarity in structure and physico-chemical properties alone do not constitute a sufficient basis to demonstrate that "*human health effects may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach)*", as required by Annex XI, 1.5 of the REACH Regulation. The Registrant indicates that "*based on the only difference in alkyl side group length between source and target, only limited difference (less than one order of magnitude) in mutagenicity, reproductive/developmental and repeated dose toxicity can be expected*". ECHA considers that the claim of limited impact of the structural differences between the source and registered substances on the properties under consideration in this read-across approach is not adequately supported by scientific arguments, since there are chemicals where changes in alkyl chain length lead to large differences in toxicity. ECHA considers that the Registrant has not otherwise provided an acceptable basis whereby the effect of the structural differences on the properties under consideration can be predicted. ECHA considers that the Registrant has not established a credible basis whereby the human health properties of the registered substance may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group, as required by Annex XI, Section 1.5 of the REACH Regulation.

ECHA further observes that the purity of the source substance reported in the read-across justification document is [redacted]%. No further details on the composition and impurity profile of the source substance are reported. Information on the composition and impurity profile of the source substance is essential in order to assess the relevance of the information obtained from the source substance to predict properties of the target substance, taking into account the possible toxicity caused by any constituent or impurity of the target substance. In the absence of detailed information on the composition and impurity profile of the source substance, ECHA is unable to verify that there is structural similarity between the source and registered substances (specifically the compounds in the source substance which are not the major constituent sodium O,O-diisobutyl dithiophosphate) which is a requirement of Annex XI, 1.5. Further, ECHA considers that, in the absence of detailed information on the composition and impurity profile of the source substance, it has not been established that human health effects may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group, as required by Annex IX, Section 1.5 of the REACH Regulation.

Moreover, ECHA notes that no endpoint specific hypothesis establishing why the read-across can be performed has been provided and observes that the documentation included in the registration dossier does not contain information or evidence supporting the likelihood of similar toxicological properties for the endpoints repeated-dose toxicity and pre-natal developmental toxicity for the source and target substances. The Registrant has reported on estimations of the toxicokinetic behaviour of the source and target substance, established on the basis of the physico-chemical properties of these substances and concluded that "*absorption and bioaccumulation of the chemicals is not expected*". ECHA considers that estimations of toxicokinetic behaviour in this case are not an adequate basis on which to draw conclusions on toxicokinetics or toxicological properties of the substances.

The Registrant updated the registration on 4 June 2015 and provided an updated read-across document "Justification of read-across from CAS No 53378-51-1. IBP1-Na (source) to CAS No 3338-24-7, EP1-Na (target)". This justification documents contains

- further information on the manufacturing process and impurity profiles of the source and target substances including the hazard classifications of the constituents and impurities of the each substance;
- information on the pH value of solutions of different concentrations of source and target substances;
- further justification on the read-across approaches for the endpoint repeated dose toxicity and reproductive toxicity. These justifications refer to ongoing sub-chronic and pre-natal developmental toxicity studies with the source substance and to a planned screening study for reproductive and developmental toxicity with the registered substance. The Registrant explained in this justification document that this screening study is intended to strengthen the read-across approaches for both endpoints under consideration. The Registrant further indicated that the validity of the read-across hypothesis will be reassessed once the data from all these studies is available. In case the hypothesis is not verified a decision on whether proposals for performing additional studies need to be submitted to ECHA will be made.
- OECD QSAR Toolbox profiles of the source and target substances.

ECHA acknowledges the further provided information and the Registrant's statement that the planned screening study for reproductive and developmental toxicity according to the OECD test guideline 422 with the registered substance may strengthen the overall read-across approaches for the endpoints under considerations. However, ECHA points out that the evidence to support the likelihood of similar toxicological properties for the endpoints repeated-dose toxicity and pre-natal developmental toxicity is not yet available.

For these reasons also, ECHA considers that it has not been demonstrated that the human health effects of the registered substance may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group, as required by Annex XI, Section 1.5 of the REACH Regulation.

On the basis of the reason stated above, ECHA concludes that the requirements of Annex XI, Section 1.5 of the REACH Regulation have not been fulfilled. Accordingly the adaptation cannot be accepted, and it is necessary to perform testing on the registered substance.

ECHA notes that whilst the read-across adaptation proposed by the Registrant cannot be accepted for the reasons above, ECHA draws the Registrant's attention to the note for consideration included in Section II.A of this decision referring to the possibility to adapt the testing requested in this decision according to the rules of Annex XI of the REACH Regulation. ECHA further points out that none of the testing proposals for conducting a sub-chronic (90-day) repeated dose toxicity study or a pre-natal developmental toxicity on the registered substance subject to this decision needs to be re-submitted.

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

a) Examination of the testing proposal

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 or 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 submitted a testing proposal for a sub-chronic toxicity study (90 day) in rodents via the oral route (EU B.26/OECD 408) to be performed with the analogue substance sodium O,O-diisobutyl dithiophosphate (EC No 258-508-5). ECHA does not consider the read-across approach justified, i.e. the testing proposal not to be compliant with the Annex XI, 1.5. provisions, as explained above in section III.0.

The Registrant proposed testing by the oral route. In light of the physico-chemical properties of the substance (solid used in the liquid form with low vapour pressure, classified as corrosive to the skin) and the information provided on the uses and human exposure (i.e. no uses with spray application), ECHA considers that testing by the oral route is most appropriate.

The Registrant proposed testing in rats. According to the test method EU B.26/OECD 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

b) Outcome

Therefore, pursuant to Article 40(3)(c) 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). The proposed test for a sub-chronic toxicity (90-day) study (test method: OECD 408) via the oral route using the analogue substance sodium O,O-diisobutyl dithiophosphate (EC No 258-508-5) is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

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

a) Examination of the testing proposal

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 to be performed with the analogue substance sodium O,O-diisobutyl dithiophosphate (EC No 258-508-5). ECHA does not consider the read-across approach justified, i.e. the testing proposal not to be compliant with the Annex XI, 1.5. provisions, as explained above in section III.0.

The Registrant proposed testing in rat, 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 these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

b) Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is requested to carry out the following 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). The proposed test for a pre-natal developmental toxicity study in rats (test method: EU B.31/OECD 414) via the oral route using the analogue substance sodium O,O-diisobutyl dithiophosphate (EC No 258-508-5) is rejected pursuant to Article 40(3)(d) of the REACH Regulation

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.