~~Confidential~~

Helsinki, 11 February 2022

Addressees
Registrants of JS_201-111-9 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
29/07/2020

Registered substance subject to this decision ("the Substance")
Substance name: Diethyl ethylphosphonate
EC number: 201-111-9
CAS number: 78-38-6

Decision number: Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/F)

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***19 May 2023***.

Requested information must be generated using the Substance unless otherwise specified.

A. Information required from all the Registrants subject to Annex VII of REACH

1. Skin sensitisation (Annex VII, Section 8.3.):

   i. In vitro skin sensitisation information on activation of dendritic cells (test method: EU B.71/OECD TG 442E)(Annex VII, Section 8.3.1.);

   and

   ii. Robust study summaries for *In chemico* Direct Peptide Reactivity Assay (OECD TG 442C) and *in vitro* ARE-Nrf2 Luciferase Test Method (OECD TG 442D;

   and

   iii. Only if the in vitro/in chemico test methods specified under point 1.i and ii. are not applicable for the Substance or the results obtained are not adequate for classification and risk assessment, in vivo skin sensitisation (Annex VII, Section 8.3.2.; test method: EU B.42./OECD TG 429

2. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: EU C.2./OECD TG 202)

3. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: EU C.3./OECD TG 201)

B. Information required from all the Registrants subject to Annex VIII of REACH

1. Short-term repeated dose toxicity (28 days; Annex VIII, Section 8.6.1.) to be combined with the Screening for reproductive/developmental toxicity below

2. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.64/OECD TG 422) by oral route, in rats

3. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: OECD TG 203)

4. Hydrolysis as a function of pH (Annex VIII, Section 9.2.2.1.; test method: EU C.7./OECD TG 111)

Reasons for the request(s) are explained in the following appendices:

- Appendix entitled "Reasons common to several requests";
- Appendices entitled "Reasons to request information required under Annexes VII to VIII of REACH", respectively.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

To comply with your information requirements you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Mike Rasenberg, Director of Hazard Assessment

[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 on Reasons common to several requests

1. **Assessment of your (Q)SAR adaptation under Annex XI, Section 1.3**

You seek to adapt the following standard information requirements by applying a (Q)SAR approach in accordance with Annex XI, Section 1.3:

- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

ECHA has considered the scientific and regulatory validity of your (Q)SAR adaptation(s) in general before assessing the specific standard information requirements in the following appendices.

Under Annex XI, Section 1.3., the following conditions must be fulfilled whenever a (Q)SAR approach is used:

1. the prediction needs to be derived from a scientifically valid model,
2. the substance must fall within the applicability domain of the model,
3. results need to be adequate for the purpose of risk assessment or classification and labelling, and
4. adequate and reliable documentation of the method must be provided.

With regard to these conditions, we have identified the following issues:

A. The substance is outside the strcutural domain of the model.

Under ECHA Guidance R.6.1.5.3., a prediction is within the applicability domain of the model, when, among others, the substance falls within descriptor, structural, mechanistic and metabolic domain.

Your registration dossier provides QSAR predictions for the endpoints listed above using the ECOSAR model v1.11 (EPI Suite). You assigned the Substance to the "Esters" class.

The Substance used as input for the prediction is outside the applicability domain of the model because it belongs also to the class "Esters (phosphate)".

B. Lack of or ina*dequate documentation of the prediction (QPRF)*

ECHA Guidance R.6.1.6.3 states that the information specified in or equivalent to the (Q)SAR Prediction Reporting Format document (QPRF) must be provided to have adequate and reliable documentation of the applied method. For a QPRF this includes, among others:

- the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

You have provided a QMRF and QPRF for the predictions. However, the documentation of your adaptation does not provide any information on close analogues used for the prediction. In addition, you have not provided any estimate of the prediction accuracy (e.g. R2) for the selected model.

Independent of issue A. above, in the absence of such information ECHA cannot establish that the prediction can be used to meet this information requirement.

On this basis, your adaptations for the endpoints listed above are rejected.

Appendix A: Reasons to request information required under Annex VII of REACH

1. Skin sensitisation

Skin sensitisation is an information requirement under Annex VII to REACH (Section 8.3.). Under Section 8.3., Column 1, the registrants must submit information allowing (1) A) a conclusion whether the substance is a skin sensitiser and B) whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A), and (2) risk assessment, where required.

You have provided the following information in the technical dossier:

i. *In chemico* Direct Peptide Reactivity Assay (DPRA) (key study, OECD TG 442C, GLP, 2018)
ii. *in vitro* ARE-Nrf2 Luciferase Test Method (LuSens) (key study, OECD TG 442D, GLP, 2018)

We have assessed this information and identified the following issues:

A) Assessment whether the Substance causes skin sensitisation

a) Missing information on key events

The information from *in vitro/in chemico* test method(s) provided must address all three key events listed under Column 1 (a) molecular interaction with skin proteins; b) inflammatory response in keratinocytes; c) activation of dendritic cells), unless information from test methods addressing one or two of these key events allows classification and risk assessment (Section 8.3.1. Column 2, second paragraph of Annex VII to REACH).

Your registration dossier provides information from *in vitro/in chemico* test methods addressing only two of the required three key events.

However, in the registration dossier and in your comments on the draft decision, you have not provided any consideration why a conclusion on the skin sensitising potential of the Substance can be met based on the studies you have been provided.

ECHA notes that *in vitro* skin sensitisation information on the activation of dendritic cells is lacking.

Therefore, the data provided do not cover all the key events set in the Annex VII, Section 8.3.1 and does not allow to make a conclusion whether the Substance causes skin sensitisation.

b) Reporting of in vitro studies

Article 3(28) defines a robust study summary as a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study minimising the need to consult the full study report. Information on the reporting needs are specified in the respective OECD test guidelines under section "Test report".

In your dossier the robust study summaries that you have submitted for the studies OECD TG 442C and 442D do not contain the information that is required by the test guidelines under section "Test Report". Without this information no independent

assessment can be made.

Therefore the studies (OECD TG 442C and TG 442D) cannot be taken into account to determine whether the Substance causes skin sensitisation.

The data provided do not cover all the key events set in the Annex VII, Section 8.3.1 or does not allow independent assessment of the information provided and therefore does not allow to make a conclusion whether the Substance causes skin sensitisation.

In your comments on the draft decision, you submitted detailed summaries of the provided studies (i) and (ii). The information you have provided in your comments gives clarity on the issue b) identified above. However, this information does not resolve the deficiencies of the robust study summaries currently provided in the dossier. The incompliances remains. You should therefore submit this information in an updated registration dossier by the deadline set out in the decision.

Based on the above, no conclusion can be made whether the Substance causes skin sensitisation.

B) Assessment whether the Substance can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

No assessment of potency

To be considered compliant and enable concluding whether the Substance causes skin sensitisation, in case the substance is considered to cause skin sensitisation the information provided must allow a conclusion whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

As the currently available data does not allow to conclude whether the Substance causes skin sensitisation (see section A above), this condition cannot be assessed.

On this basis, the information requirement is not fulfilled.

Study design

To fulfil the information requirement for the Substance for skin sensitisation, *in vitro* study (EU Method B.71/OECD TG 442E) is considered suitable. In case *in vitro* methods are not suitable for the Substance or the results cannot be used for classification and risk assessment an *in vivo* skin sensitisation study must be performed and the murine local lymph node assay (LLNA) (EU Method B.42/OEDC TG 429) is considered as the appropriate study.

2. Short-term toxicity testing on aquatic invertebrates

Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII to REACH (Section 9.1.1.).

You have adapted this information requirement under Annex XI, Section 1.3. ('QSAR'). In support of your adaptation you provided the following information: a QSAR prediction of acute Daphnia toxicity using the ECOSAR model v1.11 (EPI Suite).

However, as explained in the Appendix on reasons common to several requests, your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

3. Growth inhibition study aquatic plants

Growth inhibition study aquatic plants is an information requirement under Annex VII to REACH (Section 9.1.2.).

You have adapted this information requirement under Annex XI, Section 1.3. ('QSAR'). In support of your adaptation you provided the following information: a QSAR prediction of toxicity to alage using the ECOSAR model v1.11 (EPI Suite).

However, as explained in the Appendix on reasons common to several requests, your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

Appendix B: Reasons to request information required under Annex VIII of REACH

1. Short-term repeated dose toxicity (28 days)

A Short-term repeated dose toxicity study (28 days) is an information requirement under Annex VIII to REACH (Section 8.6.1.).

You have provided the following information for this endpoint in your dossier:

i. A key study according OECD TG 422 via oral route in rats with the Substance ([redacted] 2018).

We have assessed this information and identified the following issue:

To be considered compliant and enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL), a study has to meet the requirements of OECD TG 407. The following key parameter(s) of this test guideline include

- highest dose level should aim to induce some systemic toxicity, but not death or severe suffering
- examination organ weights and histopathology

However, the highest dose level (150 mg/kg bw/d) in the study (i) did not induce any systemic toxicity. You derived a NOAEL of 150 mg/kg bw/d for systemic toxicity. Furthermore, you did not provide any justification for the selection of the highest dose level. Therefore, the dose level selection was too low, and the study does not fulfil the criterion set in OECD TG 407. In addition, the reporting of study is unclear, deficient and partly contradictory, i.e. it is not clear whether organ weights were recorded and histopathological examination performed.

In your comments, you submitted a full study report on the study (i). The information you have provided in your comments gives clarity on the issue identified above. However, this information does not resolve the deficiencies of the robust study summaries currently available in your registration dossier. Therefore, the incompliance remains. You should therefore submit this information in an updated registration dossier by the deadline set out in the decision.

On this basis, the information requirement is not fulfilled.

Study design

Referring to the criteria in Annex VIII, Section 8.6.1, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity, because the Substance is a liquid with a low vapour pressure (0.72 kPa).

Therefore the sub-acute toxicity study must be performed according to the OECD TG 407, in rats and with oral administration of the Substance.

When there is no information available neither for the 28-day repeated dose toxicity endpoint (OECD TG 407) nor for the screening study for reproductive/developmental toxicity (OECD TG 421) (see Appendix B.2.), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to avoid unnecessary animal testing and because it fulfils the information requirement in both Annex VIII, Section 8.6.1. and 8.7.1. of REACH (ECHA Guidance R.7.6.2.3.2.).

2. Screening for reproductive/developmental toxicity

A Screening for reproductive/developmental toxicity study (test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) is an information requirement under Annex VIII to REACH (Section 8.7.1.), if there is no evidence from analogue substances, QSAR or *in vitro* methods that the Substance may be a developmental toxicant. There is no information available in your dossier indicating that your Substance may be a developmental toxicant.

You have provided the following information for this endpoint in your dossier:

i. A key study according OECD TG 422 via oral route in rats with the Substance ([redacted] 2018).

We have assessed this information and identified the following issue:

To be considered compliant and to generate information concerning the effects of the Substance on male and female reproductive performance as well as specific target organ toxicity, the study has to meet the requirements of EU B.64/OECD TG 422. The criteria of this test guideline include for example:

- highest dose level should aim to induce toxic effects;
- examination of histopathology including reproductive organs and tissues in parental animals;
- examination of offspring parameters such as number and sex of pups, stillbirths and live births, gross abnormalities, litter weight, anogenital distance, and number of nipples/areolae in male pups.

However, the highest dose level (150 mg/kg bw/d) in the study (i.) did not induce any toxicity and you have not shown that the aim was to induce toxicity. Therefore, the dose level selection was too low, and the study does not fulfil the criterion set in EU B.64/OECD TG 422. The reporting of study is unclear, deficient and partly contradictory. You have derived a NOAEL (systemic toxicity, parental animals) of 50 mg/kg bw/d based on effects in body weight and weight gain. However, in the result section you state that no significant effects on body weight and weight gain were observed. In addition, in the study (i.), examination of histopathology in parental animals and investigations for number and sex of pups, stillbirths and live births, gross abnormalities, litter weight, anogenital distance, and number of nipples/areolae in male pups have not been performed as required in EU B.64/OECD TG 422.

On this basis, the information requirement is not fulfilled.

In your comments, you submitted a full study report on the study (i). The information you have provided in your comments gives clarity on the issue identified above. However, this information does not resolve the deficiencies of the robust study summaries currently available in your registration dossier. Therefore, the incompliance remains. You should therefore submit this information in an updated registration dossier by the deadline set out in the decision.

Study design

When there is no information available neither for the 28-day repeated dose toxicity endpoint (OECD TG 407) nor for the screening study for reproductive/developmental toxicity (OECD TG 421/422), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to avoid unnecessary animal testing and because it fulfils the information requirement in both Annex VIII, Section 8.6.1. and 8.7.1. of REACH (ECHA Guidance R.7.6.2.3.2.).

Therefore, a study according to the test method EU B.64/OECD TG 422 must be performed in rats with oral administration (ECHA Guidance R.7.6.2.3.2) of the Substance.

2. Short-term toxicity testing on fish

Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.).

You have adapted this information requirement under Annex XI, Section 1.3. ('QSAR'). In support of your adaptation you provided the following information: a QSAR prediction of acute fish toxicity using the ECOSAR model v1.11 (EPI Suite).

However, as explained in the Appendix on reasons common to several requests, your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

3. Hydrolysis as a function of pH

Hydrolysis as a function of pH is an information requirement under Annex VIII to REACH (Section 9.2.2.1.).

You registration dossier provides a study according to OECD TG 111 on the Substance.

We have assessed this information and identified the following issues:

A robust study summary must be provided for the sole study available or, if more than one is available, for the study/ies giving rise to the highest concern (Articles 3(28) and 10(a)(vii) and Annex I, Section 3.1.5 of REACH).
A robust study summary must cover sufficient and consistent information to make an independent assessment of the study, including replicate data and means in tabular form and all original data and figures.

However, the study summary you provided does not include this critical information, in particular Figures 6 to 10 and Table 3 referred to in the 'results and discussion: preliminary study' section of your robust study summary are not provided.

Furthermore, the study summary contains contradictory information:
In the "results and discussion" section of your dossier you state that '*The results of the preliminary test showed that the test substance concentration decreased for pHs 7 and 9, indicating that the test substance is stable at pH 4, but unstable at pHs 7 and 9*.' However, in the applicant's summary and conclusion section of the dossier you state the converse: '*the test substance (Diethyl ethylphosphonate) did not degrade more than 10% of the initial concentration at 50 ± 0.5°C at pHs 7 and 9, but at pH 4 the concentration of the test substance decreased from the initial concentration*.'

Therefore, it is not possible to make an independent assessment of the study/ies.

To allow such assessment, you need to provide a complete robust study summary with the above missing elements for the study.

Alternatively, if you cannot submit a complete RSS or the RSS indicates that the study is not reliable or adequate to fulfil the information requirement, you need to submit the following study for the Substance: Hydrolysis as a function of pH (test method: EU C.7./OECD TG 111).

In your comments on the draft decision you confirmed that at pH 4 the substance degraded by >10% in the Tier 1 preliminary test and you provided a summary of the Tier 2 test at pH 4. You also provided further information on the Tier 1 preliminary test. ECHA has assessed the information against the requirement in OECD TG 111. The information you have provided in your comments provides clarity on the issues identified above. However, this information does resolve the deficiencies of the robust study summaries currently available in your registration dossier. Therefore, the incompliance remains. You should therefore submit this information in an updated registration dossier by the deadline set out in the decision

On this basis, the information requirement is not fulfilled.

Appendix C: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[2].

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. Selection of the Test material(s)

   The Test Material used to generate the new data must be selected taking into account the following:
   - the variation in compositions reported by all members of the joint submission,
   - the boundary composition(s) of the Substance,
   - the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

2. Information on the Test Material needed in the updated dossier
   - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[3].

[2] https://echa.europa.eu/practical-guides
[3] https://echa.europa.eu/manuals

Appendix D: Procedure

This decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 20 May 2020.

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

ECHA took into account your comments and did not amend the requests.

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix E: List of references - ECHA Guidance[4] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[5]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[6]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[7]

[4] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[5] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[6] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[7] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

Appendix F: Addressees of this decision and their corresponding information requirements

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.