~~Confidential~~

Helsinki, 17 August 2021

Addressees
Registrants of JS_diethyl_oxalate as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
14/11/2018

Registered substance subject to this decision ("the Substance")
Substance name: Diethyl oxalate
EC number: 202-464-1
CAS number: 95-92-1

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 ***25 May 2023***.

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

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

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.; test method: OECD TG 408) by oral route, in rats, with the additional parameters found in Annex A1.

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rabbit)

3. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: OECD TG 210)

Reasons for the requests are explained in the following appendices:

- Appendix entitled "Reasons common to several requests";
- Appendix entitled "Reasons to request information required under Annex IX of REACH".

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, VIII and IX to REACH, for registration at 100-1000 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". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations 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 Christel Schilliger-Musset, 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 read-across approach under Annex XI, Section 1.5.**

You seek to adapt the following standard information requirements by applying (a) read-across approach(es) in accordance with Annex XI, Section 1.5:

- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

ECHA has considered the scientific and regulatory validity of your read-across approach(es) in general before assessing the specific standard information requirements in the following appendices.

Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (addressed under 'Assessment of prediction(s)').

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6. and related documents[2,3].

A. Predictions for toxicological properties

You have provided a read-across justification document in IUCLID Sections 7.51 and 7.8.2.

You read-across between the structurally similar substance, Oxalic acid (EC No. 205-634-3, CAS No. CAS 144-62-7) as source substance and the Substance as target substance.

You have provided the following reasoning for the prediction of toxicological properties:
"The hypothesis for the analogue approach is mainly based on the fact that Diethyl oxalate (DEO) hydrolyses rapidly to Monoethyl oxalate and Oxalic acid in water […] Due to the expected hydrolysis in the gastrointestinaltract it can be assumed that DEO decomposes completely into its hydrolysis products during the passage through the stomach (pH < 4) and the intestine (pH 6-8) […] The validity of the proposed read across is further strengthened by the structural similarity and related physico-chemical properties of the target and source chemical".

ECHA understands that you predict the properties of the Substance using a read-across hypothesis which is based on the formation of common (bio)transformation products. The properties of your Substance are predicted to be quantitatively equal to those of the source substance.

ECHA has analysed the provided information and identified the following issues:

1. *Missing consistent and supporting information on toxicokinetic (hydrolysis)*

[2] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)
[3] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://doi.org/10.2823/794394

Annex XI, Section 1.5 of the REACH Regulation states that "*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*". For this purpose "*it is important to provide supporting information to strengthen the rationale for the read-across*"[4]. The set of supporting information should be consistent and allow to verify the crucial aspects of the read-across hypothesis, as well as, to establish that the properties of the Substance can be predicted from the data on the source substance(s).

Supporting and consistent information must include, among others toxicokinetic information on the formation of the common compound, information on the impact of non-common compounds.

However, as indicated above, your read-across hypothesis is based on the (bio)transformation of the Substance to the source substances as a common compound(s). One important aspect in establishing that substances have similar effects or follow a regular pattern is the comparison of absorption, distribution, metabolism and elimination (ADME) of the substances.

In your registration dossier you have not provided any information from toxicokinetic studies which would allow such a comparison. You claim that due to similar physicochemical properties "*it is considered that the toxicokinetic behaviour of the substances (and hydrolysis products) can be expected to be similar*".

In order to establish the rapid hydrolysis of your Substance to the source substance, you have provided an OECD TG 111 study, in which the hydrolysis half-lives measured at pH 4 are reported as follows: $t_{1/2}$ approx. 1.8 days (20 °C), $t_{1/2}$ approx. 0.5 day (35 °C) and $t_{1/2}$ approx. 0.2 day (50 °C). The identified hydrolysis products are monoethyloxalate (initial degradation product), ethanol and oxalate (final degradation product). Further, in your justification document you state that "*Due to the expected hydrolysis in the gastrointestinal tract it can be assumed that DEO decomposes completely into its hydrolysis products during the passage through the stomach (pH < 4) and the intestine (pH 6-8)".*

First, ECHA notes that the hydrolysis of the Substance is a step-wise process with an initial degradation product monoethyloxalate, which is identified after 1h of incubation at room temperature and that the hydrolysis half life at pH 4 is 0.5 day at 35 °C. This information indicates that hydrolysis is not sufficiently rapid as to allow exposure to the substance and initial metabolites to be excluded from consideration. Furthermore, the test conditions (pH and temperature) of the study do not resemble those in the gastro-intestinal tract (GIT) (pH < 2 and 37°C).

Therefore, the results are not sufficient to support your claim of rapid hydrolysis in the GIT.

Differences in the hydrolysis kinetics at different pHs could lead to differences in the systemic availability of the parent substances and their hydrolysis products and, consequently may result in different the toxicity of the target and source substances.

2. Missing information on the impact of non-common compounds

As indicated above, your read-across hypothesis is based on the two-step (bio)transformation of the Substance to the source substance as a common compound. In this context, exposure to the Substance and of the source substance(s) may also lead to exposure to other compounds than the common compound of interest. The impact of exposure to these non-

[4] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

common compounds on the prediction of properties of the target needs to be assessed to ensure that a reliable prediction can be made.

In your justification document you state that the Substance undergoes step-wise biotransformation to monoethyl oxalate and ethanol (as intermediate metabolites) and to oxalic acid (the final metabolite).

However, you have not provided information characterising the exposure to the intermediate non-common compounds resulting from exposure to the Substance and of the source substance(s). No experimental data or other adequate and reliable information addressing the impact of exposure to these non-common compounds is included in the documentation of your read-across approach. In the absence of such information, you have not established that a reliable prediction of the property under consideration of the Substance can be derived on the basis of your read-across hypothesis. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

In your comments to the draft decision you express your understanding that it is important to further substantiate your hypothesis, and you present a tier-based testing strategy that relies on the generation of additional information to support it. Depending on the obtained results, you discuss two scenarios: (i) if the testing would provide sufficient information to support the read across hypothesis, no further testing will be needed and (ii) if the testing "*would not sufficiently explain the differences between DEO* [the Substance] *and oxalate in repeated dose toxicity"* then you would perform the requested tests.

ECHA acknowledges your intentions to improve the toxicological profile of the Substance and your plans to refine your read-across approach. As indicated in your comments, this strategy relies essentially on data which is yet to be generated, no conclusion on the compliance can currently be made, as this is work in progress. You remain responsible for complying with this decision by the set deadline.

B. Conclusions on the read-across approach

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the analogue substance. Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

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

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

A Sub-chronic toxicity study (90 day) is a standard information requirement in Annex IX to REACH.

You have adapted the standard information requirement in accordance with Annex XI, section 1.5. to REACH by providing the justification discussed in the Appendix on Reasons common to several requests above (section 1, read-across) and the following study records:

With the Substance:

(i) 28 Days repeated-dose toxicity study in rats (oral). [redacted] 2011. According to OECD TG 407.

With the source substance Oxalic acid (EC No. 205-634-3, CAS No. CAS 144-62-7):

(ii) 90 Days repeated-dose toxicity study in rats (oral). [redacted] 2017. According to OECD TG 408.

ECHA assessed this information and identified the following issues:

A. Invalid read-across hypothesis concerning study (ii)

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

B. Non-conformity of study (i) with the specifications of the applicable test guideline

To fulfil the information requirement, a study must comply with the OECD TG 408 (Article 13(3) of REACH). Therefore, the following specifications must be met:
- exposure duration of 90 days;
- 20 animals (10 males + 10 females) for each test group.

However, the repeated-dose oral toxicity study (OECD TG 407) you provided does not have an exposure duration of 28 days and was conducted with less than 10 animals per sex per test dose group.

In your comments to the draft decision you did not provide any new information for this information requirement. You state that you "*would like to focus on the substantiation of the read-across between DEO and oxalate"* as explained in the testing strategy.

As explained in the Appendix on Reasons common to several requests, this strategy relies essentially on data which is yet to be generated.

Based on the above, the information you provided do not fulfil the information requirement.

Information on the design of the study to be performed (route/ species)

Referring to the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity, because although the information indicate that human exposure to the Substance by the inhalation

route is likely (PROC 7, PROC 11), potential inhalation-specific effects are already addressed by deriving a long-term DNEL for inhalation.

Therefore the sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration of the Substance.

Additional parameters

Detailed investigations of reproductive organs must be conducted to further investigate the effects in reproductive organs observed in the OECD TG 421 study. Therefore the study must include, in addition to the default investigations of OECD TG 408, all the optional investigations from paragraphs 39-40 (enumeration of cauda epididymis sperm reserves, sperm morphology and sperm motility) and paragraph 45 (preservation of testes by immersion in Bouin's or Davidson's fixative and staging of seminiferous tubulus cross sections). Oestrus cycles must be investigated by taking vaginal smears for two weeks before the termination and ovarian histopathology must follow the specification in paragraph 73 of OECD TG 443. Furthermore, it is recommended that the potential dose-depent presence of oxalate crystals in reproductive organs as well as in kidneys is investigated.

2. Pre-natal developmental toxicity study in one species

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX to REACH.

You have adapted the standard information requirement in accordance with Annex XI, section 1.5. to REACH by providing the justification discussed in the Appendix on Reasons common to several requests above (section 1, read-across) and the following study records:

With the Substance:

(i) Reproduction Developmental Toxicity Screening Test in rats. [redacted] 2011. According to OECD TG 421.

With the substance Oxalic acid (EC No. 205-634-3, CAS No. CAS 144-62-7):

(ii) Prenatal developmental toxicity study in rabbits. [redacted] 2017. According to OECD TG 414.

ECHA assessed this information and identified the following issues:

A. Invalid read-across hypothesis concerning study (ii)

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

B. Non-conformity of study (i) with the specifications of the applicable test guideline

To fulfil the information requirement, a study must comply with the OECD TG 414 (Article 13(3) of REACH). Therefore, the following specifications must be met:
- structural malformations and variations must be investigated.

However, the OECD TG 421 study you provided in your dossier does not investigate structural malformations and variations.

In your comments to the draft decision you did not provide any new information for this endpoint. You state that "*if the read-across to oxalic acid can be substantiated further (see 1.1.), no additional animal studies would be required*".

As explained in the Appendix on Reasons common to several requests, this strategy relies essentially on data which is yet to be generated.

Based on the above, the information you provided do not fulfil the information requirement.

Information on the design of the study to be performed

A PNDT study according to the test method OECD TG 414 must be performed in the rabbit as preferred species with oral[5] administration of the Substance.

Based on the available information, higher dose levels without kidney toxicity may be reached in rabbits rather than in rats. This is important for investigating the intrinsic properties of the Substance for prenatal developmental toxicity.

In your comments to the draft decsion you argue that if oxalate nephrotoxicity is the most sensitive effects and "*if rabbits aren't more sensitive to oxalate-based kidney effects, there is no justification to further investigate other intrinsic properties in animal studies at doses that would be much higher than the DNEL or NOAEL, which are already derived based on the most critical / sensitive effect".*

ECHA agrees that the kidney effect seems to be the most critical to derive DNEL for the purpose of risk assessment for systemic toxicity. However, for the purpose of hazard identification, relevant and reliable information for the developmental toxicity potential of the Substance is needed. According to OECD TG 414 a PNDT study should be performed in rat or rabbit as preferred species. Based of the higher sensitivity of the rat to the kidney effects that occur at relatively low doses, maternal toxicity in rats may limit the dose selection and thereby a meaningful evaluation of developmental toxicity of the Substance. Since kidney effects are not reported in the rabbit at higher dose levels, ECHA considers it as preferred species to generate data that would inform on the developmental hazard of the Substance.

Therefore, the OECD TG 414 study must be performed in rabbits.

3. Long-term toxicity testing on fish

Long-term toxicity testing on fish is an information requirement under Annex IX to REACH (Section 9.1.6.).

You have provided a justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2. In support of your adaptation, you provided the following justification regarding the substance (CAS 95-92-1):

- Hazard assessment shows that no classification is needed for environmental hazard and
- No PBT or vPvB concern was raised

We have assessed this information and identified the following issue:

Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to fish under Column 1. It must be understood as a trigger for providing

[5] ECHA Guidance R.7a, Section R.7.6.2.3.2.

further information on long-term toxicity to fish if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

In your comments, you submitted an adaptation under Annex XI, Section 3.1 ('Substance-tailored exposure driven-testing') with the following justification: *"RCR determined for all compartments in this risk assessment is* [redacted]*"*. ECHA has assessed this information and concluded that the information provided in your comments addresses the incompliance identified in the draft decision. However, as the adaptation is currently not explicitly specified in your registration dossier, the data gap 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

To fulfil the information requirement for the Substance, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (ECHA Guidance R.7.8.2.).

The Substance is difficult to test due as it is rapidly hydrolyses ($t_{1/2}$, 20 °C is approximately 1.8 days at pH 4, rapid hydrolysis at pH 7 and 9. OECD TG 210 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 210. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

Appendix B: 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[6].

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[7].

[6] https://echa.europa.eu/practical-guides
[7] https://echa.europa.eu/manuals

Appendix C: Procedure

The information requirement for an Extended one-generation reproductive toxicity study (EOGRTS; Annexes IX or X, Section 8.7.3.) is not addressed in this decision. This may be addressed in a separate decision once the information from the Sub-chronic toxicity study (90-day) requested in the present decision is provided; due to the fact that the results from the 90-day study is needed for the design of the EOGRTS.

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 22 June 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.

In your comments on the draft decision, you request an extension of the deadline to provide the information set out in this decision by 9 months in order to provide the additional information justifying a tiered testing. Testing proposals in accordance with Article 40 of the REACH Regulation aim at assessing whether a testing strategy meet a real information need while compliance checks under Article 41 aim at bringing dossier into compliance with the information requirements set out under Annex VII to X of REACH. Therefore, it is not the purpose of the present decision to evaluate the testing strategy proposed by the registrant and the deadline for submitting the requested information cannot be postponed.

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 D: List of references - ECHA Guidance[8] 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)[9]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[9]

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[10]
Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

[8] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[9] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[10] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

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 E: 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]
[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.