Helsinki, 13 September 2018

Addressee: [redacted]

Decision number: CCH-D-2114440090-66-01/F
Substance name: 2,2'-oxybis-ethanol diformate
EC number: 601-722-4
CAS number: 120570-77-6
Registration number: [redacted]
Submission number: [redacted]
Submission date: 22/04/2013
Registered tonnage band: 100-1000

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. **Spectral data (Annex VI, Section 2.3.5.) on the registered substance;**
   - **Nuclear magnetic resonance or mass spectrum**
2. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. / OECD TG 471) with the registered substance, ;**
3. **In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method: OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2, test method: OECD TG 487) with the registered substance;**
4. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance, provided that both studies requested under 2. and 3. have negative results;**
5. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats with the registered substance;**
6. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD TG 421/422) in rats, oral route with the registered substance;**
7. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

You 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 to the REACH Regulation. To ensure compliance with the respective information requirement, any such

adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by ***22 March 2021***. You also have to update the chemical safety report, where relevant.

The reasons of 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 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.

Appendix 1: Reasons

IDENTIFICATION OF THE SUBSTANCE

In accordance with Article 10(a)(ii) of the REACH Regulation, the technical dossier must contain information on the identity of the substance as specified in Annex VI, Section 2 to the REACH Regulation. In accordance with Annex VI, Section 2 the information provided has to be sufficient to enable the identification of the registered substance.

1. Spectral data (Annex VI, Section 2.3.5.)

In accordance with Article 10(a)(ii) of the REACH Regulation, the technical dossier must contain information on the identity of the substance as specified in Annex VI, Section 2 to the REACH Regulation. In accordance with Annex VI, Section 2 the information provided has to be sufficient to enable the identification of the registered substance.

"Spectral data" are a formal information requirement as laid down in Annex VI, Section 2.3.5 of the REACH Regulation. Adequate information needs to be present in the technical dossier to confirm the composition of the substance and thus its identity.

The nuclear magnetic resonance (NMR) spectrum submitted in the registration dossier was not recorded on the substance subject to the present decision. Therefore the registration dossier does not contain a full set of analytical data for the registered substance as required under Annex VI Section 2.3.5 of the REACH Regulation.

ECHA regards this required information scientifically necessary for the identification of the registered substance. Without such information, the identity of the substance cannot be verified.

Therefore, you are requested to submit a NMR (or, alternatively MS spectrum) generated on the manufactured substance subject to the present decision. A full interpretation of the spectrum, including peak assignment, should be provided in order to confirm the structure of the substance. In addition, you are requested to provide, in the dossier, the description of the analytical methods used for recording the spectrum in such detail to allow the method to be reproduced, in line with the requirements under Annex VI Section 2.3.7 of the REACH Regulation. You shall ensure that the information is consistent with the information provided throughout the dossier.

Regarding how to report the spectral data, the information shall be attached in section 1.4 of the IUCLID dossier.

TOXICOLOGICAL INFORMATION

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Your registration dossier contains for multiple endpoints adaptation arguments in the form of a grouping and read-across approach according to Annex XI, 1.5. of the REACH Regulation. ECHA has assessed first the scientific and regulatory validity of your Grouping and read-across approach in general before the individual endpoints (sections 2 to 7).

Grouping and read-across approach for toxicological information

You have sought to adapt information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5, for the endpoints:

- *in vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- *in vitro* cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- *in vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- sub-chronic toxicity (90-day) study (Annex IX, Section 8.6.2.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. 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 (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances[2]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus, physicochemical and degradation properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical and degradation properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.
The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[3]- (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.
[3] Please see ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

i. Description of the grouping and read-across approach proposed by you

You consider to achieve compliance with the REACH information requirements for the registered substance diethyleneglycol diformate (EC number: 601-722-4; CAS RN 120570-77-6) using data of structurally similar substances (1) ethylene glycol diformate (EC number 211-077-7; CAS RN 629-15-2), (2) ethylene glycol (EC number 203-473-3; CAS RN 107-21-1), (3) diethylene glycol (EC number 203-872-2; CAS RN 111-46-6), (4) formic acid (EC number 200-579-1; CAS RN 64-18-6) and its salt (5) sodium formate (EC number 205-488-0; CAS RN 141-53-7) (hereafter the 'source substances'). *"Diethyleneglycol diformate is the diester of the diol diethylene glycol with the carboxylic acid formic acid."*

You have provided a read-across documentation as a separate attachment.

You use the following arguments to support the prediction of properties of the registered substance from data for source substances within the group: (1) Similar structure and common functional groups, (2) similar physico-chemical properties, (3) similar toxicological properties (mammalian toxicity profiles), and (4) the registered substance breaks down into formic acid, diethylene glycol, which subsequently breaks down into ethylene glycol; that the properties of these are similar, and these source substances can predict the properties of the registered substance.

As an integral part of this prediction, you propose that the source and registered substance(s) have similar mammalian toxicity profiles for the above-mentioned information requirements. Therefore you consider that you can predict the properties of the registered substance for toxicological properties, relying on the information on source substances. ECHA considers that this information is your read-across hypothesis.

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

With regard to the proposed predictions ECHA has the following observations:

The substance characterisation of the source substances need to be sufficiently detailed in order to assess whether the attempted prediction is not compromised by the composition and/or impurities. In the ECHA's Practical Guide on "How to use alternatives to animal testing to fulfil your information requirements" (chapter 4.4), it is recommended to follow the ECHA *Guidance for identification and naming of substances under REACH and CLP* (version 2.1, May 2017) also for the source substances.

This ensures that the identity of the source substance and its impurity profile allows an assessment of the suitability of the substances for read-across purposes. Currently the identity of the source substances (and their impurity profile) are not sufficiently detailed in the registration dossier.

Your proposed adaptation argument is that the similarity in chemical structure and in some of the physico-chemical and toxicological properties between the source and registered substance is a sufficient basis for predicting the properties of the registered substance for other endpoints. Structural similarity is a prerequisite for applying the grouping and read-across approach. However similarity in chemical structure and similarity of some of the physico-chemical and toxicological properties does not necessarily lead to predictable or similar human health properties in other endpoints.

Your adaptation argument (4) is that the properties of the registered substance can be predicted from the properties of the breakdown products. However, as set out above, it is not possible to consider that the breakdown products will have similar toxicological properties as a result of structural, physicochemical or toxicological similarities. Thus ECHA considers that is implicit in your adaptation argument that the registered substance breaks down to the source substances rapidly, and so the body is only exposed to the source substances.

While ECHA considers it is plausible that diethylene glycol diformate may break down to diethylene glycol and formic acid, you do not properly quantify how "rapid" is the breakdown of the registered substance to the source substances, and additionally, you have not addressed how quickly (or to what extent) the diethylene glycol breaks down to the ethylene glycol (this is a subsequent step after the first step in the pathway).

You have provided 2 sets of data to address hydrolysis:

(i) QSAR (HydroWIN) on the registered substance: at pH7, the half-life is 1.242 days and at pH8, the half-life is 2.981 hours;

(ii) an *in vitro* study (tk) on the source (1) ethylene glycol diformate (EC number 211-077-7; CAS RN 629-15-2), showing 79.7% hydrolysis after 1 hour. You concluded that there is "*Full hydrolysis within 4 hours of the test item in intestine fluid simulant at a pH value of 7.5 at 37 °C was demonstrated in this hydrolysis study. The half-life in simulated intestinal fluid was calculated to be 0.67 hours.*"

Regarding (i) ECHA considers that with such half-lives, systemic exposure of the organisms to the registered substance is likely.
Regarding (ii), ECHA considers that the data is on the source substance (1) ethylene glycol diformate (EC number 211-077-7; CAS RN 629-15-2), and it cannot be used to justify the rapid hydrolysis of the registered substance. Therefore you have not shown that the registered substance hydrolyses rapidly to formic acid and diethylene glycol. Moreover, you have not provided information about the speed of hydrolysis and quantitative conversion of diethylene glycol to ethylene glycol. Since it is not clear whether and to what extent the diethylene glycol breaks down to ethylene glycol (or other substances), ECHA considers that it is not possible to predict the properties of the registered substance from ethylene glycol. Further, your technical dossier contains only experimental data on hydrolysis at pH 7.5. In order to simulate conditions relevant to human health, such as the gastric fluid environment, information on the hydrolysis of the registered substance at a more acidic (i.e., pH 1.5) would also be necessary.

Accordingly, as the information reported in the technical dossier does not contain data on hydrolysis rates at all relevant pH values or on the hydrolysis products, it is inadequate to show rapid hydrolysis of the registered substance in the body under any circumstances.

Consequently in light of the information you have submitted, you have not demonstrated that the registered substance hydrolyses rapidly, systemic exposure to the registered substance is likely and you have not provided an adequate basis for predicting the properties of the parent, registered substance before hydrolysis, other than as its hydrolysis products. Consequently, ECHA considers you cannot reliably predict the properties of the registered substance from the source substances.

Finally you claim as a basis for prediction that that the target and the source substances have similar mammalian toxicity profiles, and that you can predict the toxicological properties of the registered substance while simultaneously conceding, for each endpoint

reviewed, that "*There are no data available [...] on diethylene glycol diformate*". ECHA considers that in absence of results from lower-tier endpoints (e.g. *in vitro* genetic toxicity, subacute toxicity, irritation, in a format of a data matrix), you cannot set the basis for a prediction in order to extrapolate to the higher tier endpoints as you cannot demonstrate that the hypothesis you are setting has been demonstrated and that prediction from reliable studies on the sources substances is possible to the human health properties of the target, registered substance. Therefore your justification based on structural similarity, similar physico-chemical and toxicological properties has not established why the prediction is reliable for the human health endpoints for which the read across is claimed.

Additionally, ECHA has taken into account all of your arguments together. ECHA firstly notes that you have not provided a reasoning as to why these arguments add to one another to provide sufficient basis for read-across. Secondly, the defects of each individual argument are not mitigated by the other arguments you have provided, and so ECHA considers that the arguments when taken all together do not provide a reliable basis for predicting the properties of the registered substance.

Therefore, ECHA considers that this grouping and read-across approach does not provide a reliable basis whereby the human health effects of the registered substance may be predicted from data for reference substance(s) within the group. Hence, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation. Hence the read-across/ analogue general approach is rejected.

As described above, further elements are needed to establish a reliable prediction for a toxicological or ecotoxicological property, based on recognition of the structural similarities and differences between the source and registered substances. This could be achieved (if it is possible) by a well-founded hypothesis of (bio)transformation to a common compound(s), or that the registered and source substance(s) have the same type of effect(s), together with sufficient supporting information to allow a prediction of human health properties.

Finally, Annex XI, Section 1.5 provides with regard to the reliability and adequacy of the source studies that in all cases the results of the read-across should:

- *be adequate for the purpose of classification and labelling and/or risk assessment,*
- *have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3),*
- *cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter, and*
- *adequate and reliable documentation of the applied method shall be provided.*

ECHA notes that if the above specific considerations result in a failure to meet the requirement of Annex XI, Section 1.5., these are set out under the endpoint concerned, namely (i) the supporting studies submitted to address the various endpoints are not fulfilling the endpoints requirements (e.g. not fulfilling the current test guidelines criteria), and (ii) you have not provided sufficient evidence (in some endpoints) to ensure full coverage of the source substances back to the target substance.

iii. Conclusion on the read-across approach

The adaptation of the standard information requirements, namely *in vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1), *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2), *in vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3), sub-chronic toxicity (90-day) study (Annex IX, Section 8.6.2.), screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1), pre-natal developmental

toxicity study (Annex IX, Section 8.7.2.), in the technical dossier is based on the proposed read-across approach examined above. For the reasons as set out above, ECHA does not consider the read-across justification to be a reliable basis to predict the properties of the registered substance.

ECHA concludes that you have failed to meet the requirement of Annex XI, Section 1.5. that human health/ environmental effects may be predicted from data of the source substances. Thus, the adaptation does not comply with the general rules of adaptation as set out in Annex XI, 1.5.

2. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

An "*In vitro* gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for an *in vitro* gene mutation study in bacteria (OECD TG 471) with the analogue substance ethylene glycol diformate (EC number 211-077-7; CAS RN 629-15-2).

However, as explained above in Appendix 1, of this decision under "Grouping and read-across approach for toxicological information", your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that the bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. of the REACH Regulation.

In your comments on the draft decision you agreed to conduct this study with the registered substance.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information, with the registered substance subject to the present decision: Bacterial reverse mutation test (test method: EU B.13/14./ OECD TG 471).

3. In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)

An "*In vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study" is a standard information requirement as laid down in Annex VIII, Section 8.4.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records (reliability 2) for an *in vitro* chromosomal aberration study (OECD TG 473) with the analogues ethylene glycol (EC

number 203-473-3; CAS RN 107-21-1) and formic acid (EC number 200-579-1; CAS RN 64-18-6).

However, as explained in Appendix 1 of this decision under "Grouping and read-across approach for toxicological and ecotoxicological information", your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that the *in vitro* mammalian chromosome aberration test (test method OECD TG 473) and the *in vitro* mammalian cell micronucleus test (OECD TG 487) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.2. of the REACH Regulation.

In your comments on the draft decision you agreed to conduct either the *in vitro* mammalian chromosome aberration test (test method: OECD TG 473) or the *in vitro* mammalian cell micronucleus study (test method: OECD TG 487) with the registered substance.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian chromosome aberration test (test method: OECD TG 473) or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487).

4. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record (reliability 2) for an *in vitro* gene mutation study in mammalian cells (OECD TG 476) with the analogue substances ethylene glycol (EC number 203-473-3; CAS RN 107-21-1) and formic acid (EC number 200-579-1; CAS RN 64-18-6).
However, as explained above in Appendix 1 of this decision under "Grouping and read-across approach for toxicological and ecotoxicological information", your adaptation of the information requirement is rejected.

Hence, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that the *in vitro* mammalian cell gene mutation tests using the *Hprt* and *xprt* genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

In your comments on the draft decision you agreed to conduct the *in vitro* mammalian cell gene mutation test (test method: OECD TG 476 or OECD TG 490) with the registered substance, provided that both studies requested under 2. and 3. give negative results.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490) provided that both studies requested under 2. and 3. have negative results.

5. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

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. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing study records for an oral 2-year non-guideline non GLP chronic study (reliability 2) with an analogue substance, diethylene glycol (EC number 203-872-2; CAS RN 111-46-6), in rat. The dossier also contains an inhalation study (reliability 2) similar to OECD 413 and GLP with deviations (no opthalmoscopic, neurobehavioural examinations, no urinalysis, no food and water consumption were performed) in rat with an analogue substance, formic acid (EC number 200-579-1; CAS RN 64-18-6). However, as explained above in Appendix 1 of this decision under "Grouping and read-across approach for toxicological and ecotoxicological information", your adaptation of the information requirement is rejected.

Furthermore, the oral 2-year study does not provide the information required by Annex IX, Section 8.6.2., because the number of animals examined per dose group for histopathology and clinical chemistry is significantly lower than in the 90 day sub-chronic toxicity study (OECD TG 408) and only male rats are used. In addition, no haematology and clinical biochemistry examinations or functional observations were performed. Therefore, there is not adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), and for this reason also, the read-across adaptation is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA Guidance on information requirements and chemical safety assessment (version 5.0, December 2016) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route, using the test method EU B.26./OECD TG 408.

In your comments on the draft decision you appreciate ECHA's view on the request to provide this study with the registered substance. However, you indicate your intention to update the registration dossier including a testing proposal for this study. ECHA underlines

that no testing proposal is required to be submitted for the information requests included in compliance check decisions, including information requests from Annexes IX and X to the REACH Regulation. Therefore, ECHA expects the information requested in the decision to be submitted in the form of an updated registration dossier by the deadline set out in the final decision. In your comments, you furthermore indicate your intention to include additional reproduction toxicity parameters in the design of the study with the registered substance. ECHA observes that it is your responsibility to include such additional parameters in the study design.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats.

Note for your consideration

ECHA notes that a revised version of OECD TG 408 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. You should test in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

6. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

"Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. No such evidence is presented in the dossier. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing two non-guideline non GLP two-generation reproductive studies with the analogue substance diethylene glycol (EC number 203-872-2; CAS RN 111-46-6).

However, as explained above in Appendix 1, of this decision under "Grouping and read-across approach for toxicological and ecotoxicological information", your adaptation of the information requirement is rejected.

Hence, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test methods OECD TG 421 and 422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with rats.

ECHA considers 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 liquid, ECHA concludes that testing should be performed by the oral route.

In your comments on the draft decision you indicate that you consider that performing this study gives no additional value once the sub-chronic toxicity study combined with a reproduction toxicity screening part and the pre-natal developmental toxicity study have been provided. ECHA would like to draw your attention the specific rules for adaptation contained in column 2 of Annex VIII, sect. 8.7.1.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Reproductive/developmental toxicity screening test (test method: OECD TG 421) **or** Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

Notes for your considerations

For the selection of the appropriate test, please consult ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.5 and 7.6 (version 6.0, July 2017).

You should also carefully consider the order of testing, especially between the requested screening study (OECD TG 421/422) and the developmental toxicity study (OECD TG 414), (request 7 below) to ensure that unnecessary animal testing is avoided, paying particular attention to the endpoint-specific guidance https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf, Section R.7.6.2.3.2., pages 484 to 485 of version 6.0 – July 2017.

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

A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a Prenatal Developmental Toxicity Study (OECD TG 414) with the analogue substance sodium formate (EC number 205-488-0; CAS RN 141-53-7) in rabbit and two non-guideline, non GLP studies with diethylene glycol (EC number 203-872-2; CAS RN 111-46-6), in rat and mouse.

However, as explained above in Appendix 1 of this decision under "Grouping and read-across approach for toxicological and ecotoxicological information", your adaptation of the information requirement is rejected.

Hence, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

ECHA considers 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 liquid, ECHA concludes that testing should be performed by the oral route.

In your comments on the draft decision you appreciate ECHA's view on the request to provide this study with the registered substance. However, you indicate your intention to update the registration dossier including a testing proposal for this study. ECHA underlines that no testing proposal is required to be submitted for the information requests included in compliance check decisions, including information requests from Annexes IX and X to the REACH Regulation. Therefore, ECHA expects the information requested in the decision to be submitted in the form of an updated registration dossier by the deadline set out in the final decision.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a first species (rat or rabbit) by the oral route.

Note for your consideration

ECHA notes that a revised version of OECD TG 414 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. You should test in accordance with the revised version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 14 September 2017.

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.

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 took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This compliance check decision does not prevent ECHA from initiating further compliance checks on the present 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 your Member State.

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 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.