EUROPEAN CHEMICALS AGENCY

Helsinki, 13 December 2019

Addressee: [redacted]

Decision number: CCH-D-2114493592-39-01/F
Substance name: 2-(2-ethoxyethoxy)ethyl acetate
EC number: 203-940-1
CAS number: 112-15-2
Registration number: [redacted]
Submission number: [redacted]
Submission date: 5 April 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. ***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) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102 with the registered substance;**

2. ***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;**

3. ***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 1. and 2. have negative results**

4. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD 421/422) in rats, oral route with the registered substance;**

5. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

6. **Update of the technical dossier using the study "Devillers, 2003, C. dubia, 7 d, RL 3" as key study showing the highest concern for the endpoint of Long-term toxicity testing on invertebrates (Annex IX section 9.1.5.),**
   or
   Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: Daphnia magna reproduction test, EU C.20./OECD TG 211) with the registered substance;

7. **Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210) with the registered substance;**

8. **Classification and labelling (Annex VI, Section 4.): Apply classification and labelling on the registered substance for long-term aquatic hazard or provide a justification for not classifying.**

You are required to submit the requested information in an updated registration dossier by ***20 September 2021***. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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 Ofelia Bercaru, Head of Unit, 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 1: Reasons

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.

TOXICOLOGICAL INFORMATION

1. 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 in Annex VII, Section 8.4.1. of the REACH Regulation.

According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA.

Other tests may be used if the conditions of Annex XI are met. More specifically, Section 1.1.2 of Annex XI provides that existing data on human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) may be used if the following conditions are met:

(1) Adequacy for the purpose of classification and labelling and/or risk assessment;
(2) Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) adequate and reliable documentation of the study is provided.

According to paragraph 13 of the current OECD TG 471 test guideline (updated 1997) at least five strains of bacteria should be used: S. typhimurium TA1535; TA1537 or TA97a or TA97; TA98; TA100; S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). This includes four strains of S. typhimurium (TA1535; TA1537 or TA97a or TA97; TA98; and TA100) that have been shown to be reliable and reproducibly responsive between laboratories. These four S. typhimurium strains have GC base pairs at the primary reversion site and it is known that they may not detect certain oxidising mutagens, cross-linking agents and hydrazines. Such substances may be detected by E.coli WP2 strains or S. typhimurium TA102 which have an AT base pair at the primary reversion site.

You have provided a test from the year 1990, equivalent to OECD TG 471 at that time and GLP compliant with an assigned reliability score of 2. However, since the test was conducted, significant changes have been made to OECD TG 471 so that additionally testing with S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) is now required. The test that you provided used [redacted], but it did not include tests with strains S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). Therefore, the provided study does not meet the current guidelines, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation.

ECHA concludes that a test using *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102 has not been submitted and that the test using one of these strains is required to conclude on *in vitro* gene mutation in bacteria.

In your comments to the draft decision you agreed that the information currently in the dossier does not fulfil the information requirement, and further testing "may be required". ECHA understands that you acknowledge the need to perform the requested study.

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.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to complete the following information derived with the registered substance subject to the present decision: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102.

2. 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 in Annex VIII, Section 8.4.2. of the REACH Regulation.

You have not provided any study record of an *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study in the dossier that would meet the information requirement of Annex VIII, Section 8.4.2.

In the IUCLID dossier you have provided the following study records:

with the registered substance:

(i) *In vivo* micronucleus test in rats (publication data: Anonymous, (1991); equivalent to OECD TG 474, non GLP compliant, your reliability score is 2). The purity of the test material is unknown. The rats were exposed via inhalation (aerosol) [redacted] Results: negative.

with the substance (2-(2-butoxyethoxy)ethanol) (EC: 203-961-6):

(ii) *In vivo* micronucleus assay in mice (publication data: [redacted]; equivalent to OECDT TG 474, GLP not specified, your reliability score is 2). The purity of the test material is 99.51%. The mice were exposed to a single application of [redacted], via oral-gavage. Results: negative.

While you have not explicitly claimed an adaptation, ECHA interprets the information you have provided as an attempt to adapt the information requirement according to Annex VIII, Section 8.4.2., column 2, and Annex XI, Section 1.5.

Section 8.4.2. of Annex VIII provides that the study does not usually need to be conducted if adequate data from an in vivo cytogenicity test are available or the substance is known to be carcinogenic category 1A or 1B or or germ cell mutagenic category 1A, 1B or 2.

ECHA has analysed the study (i) and has the following observations:

ECHA notes that there is not adequate and reliable coverage of the key parameters addressed in the corresponding test method, specifically: the test material is not clearly identified, the exposure is via inhalation (whole body) without justification for choosing this route. Further, there is no positive control used and there is no information on the criteria for dose selection. In the study summary there is no explanation why the highest concentration of 500 mg/m^3 has been chosen and there is no data on whether a range-finding study has been performed. Based on the very limited reporting of the test conditions and the results for this study in your technical dossier, there is no evidence that the test material has become systemically available after inhalation administration. Therefore, there is no proof of bone marrow exposure that would enable to validate the negative results. Based on the analysis above, ECHA considers that the study is neither adequate nor reliable. In the absence of adequate data from an in vivo cytogenicity test or relevant classification, ECHA rejects the adaptation of the information based on column 2 of Annex VIII, Section 8.4.2.

Further, ECHA understands that you intend to predict the property "in vitro cytogenicity gene mutation" of the registered substance from data obtained with the source substance (2-(2-butoxyethoxy)ethanol) in accordance to Annex XI section 1.5 of the REACH Regulation (grouping of substances and read-across approach).

ECHA has analysed your adaptation in accordance to Annex XI, 1.5. and has the following observations:

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

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.

[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.

You have provided the following documentation as separate attachment in Section 13 of the IUCLID dossier: "[redacted]", hereafter "Read-across justification document". Further, you have provided the following supporting documents: "[redacted]" and "[redacted]". The second document summarizes the conclusion of SIAR on the Diethylene glycol ether category.

In your read-across justification document you have proposed an analogue approach, that covers the following substances:

- 2-(2-butoxyethoxy)ethyl acetate (CAS: 124-17-4); EC: 204-685-9) (source 1)
- 2-(2-ethoxyethoxy)ethanol (CAS: 111-90-0; EC: 203-919-7) (source 2)
- 2-(2-butoxyethoxy)ethanol (CAS: 112-34-5; EC: 203-961-6) (source 3)

You have provided the following hypothesis of the analogue approach: *"In organisms, esters of an alcohol with an acid are anticipated to have a common metabolic fate that involves a stepwise hydrolysis of the ester bond by gastrointestinal enzymes by which the breakdown of the esters results in structurally similar chemicals, the acid component and the alcohol component.* [redacted]".

Based on this information ECHA understands that you built your hypothesis based on the structural similarity and likelihood of common breakdown products, a results of common metabolic pathway (ester hydrolysis), which can be used to predict the toxicity properties of the registered substance. ECHA considers that this information is your read-across hypothesis.

Due to the different nature of each hazard property and consequent difference in scientific considerations (e.g. key parameters, biological targets), a grouping and read-across approach must be specific to the property under consideration. Therefore, ECHA has analysed the information you have provided in light of the prediction of genotoxicity properties of the registered substance, using data from the source substance 3 (EC: 203-961-6).

ECHA notes that the analysis provided below is focussed on the properties under consideration, i.e. predictions of the outcome of *in vitro* genotoxicity studies. Therefore your grouping and read-cross arguments relevant to properties involving systemic toxicity are not addressed in this decision.

ECHA has observed the following:

a) Explanation on why and how the structural similarities allow predictions

In order to meet the provisions in Annex XI, Section 1.5. to predict human health effects from data for a reference substance within the group by interpolation to other substances in the group, ECHA considers that structural similarity alone is not sufficient. It has to be justified why such prediction is possible in view of the identified structural differences and

the provided evidence has to support such explanation. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible.

ECHA notes that the registered and the source 3 substances differ in structure: the registered substance is an ethoxyethoxy ethyl ester while the source substance is a buthoxyethoxy ethanol. You did not explain why the different functional groups (ester and alcohol) as well as the difference in chain length (ethoxy and butoxy) would not influence the genotoxicity profiles of the source and the registered substances.

Further, ECHA understands that one element of your read-across hypothesis is the postulation that the target and the source substance 1 undergo "*a high extent hydrolysis*" to free glycol alcohols, respectively: 2-(2-ethoxyethoxy)ethanol (source substance 2) and 2-(2-butoxyethoxy)ethanol (source substance 3) and acetic acid. You further state that the glycol alcohols are expected to undergo oxidative metabolism in the liver.
ECHA notes that the source substance 3, from which you proposed to predict the properties under consideration, is not one of the metabolites of the registered substance after hydrolysis.

Further, ECHA points out that *in vitro* genotoxicity studies are performed in modules with and without metabolic activation, in order to assess the genotoxicity profile of both, the parent substance and its metabolites. Any considerations on *in vivo* metabolism involving enzymatic processes therefore are not relevant at all for a module without metabolic activation. Any prediction for the outcome of a genotoxicity study must address the properties of both the parent substance and its metabolites. You did not explain how the properties of the source substance 3, which is not among the metabolites of the registered substance, could be used to predict the genotoxicity profiles of both the parent substance and its metabolites.

Based on the analysis above, ECHA concludes that you have not addressed the obvious structural differences between the source substances and the target substance and did not explain why those differences would not lead to differences in the genotoxicity profile of target and source substances. The provided explanation is not considered as valid to establish a scientific credible link between the structural similarity and the prediction.

Furthermore ECHA notes that there is no further supporting information, such as mechanistic information or data matrix information on genotoxicity for in vitro cytogenicity in mammalian cells for the source or the target substance.

b) Reliability and adequacy of the source studies

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 has analyzed the study (ii) for its reliability and adequacy and has the following observations:

ECHA notes that there is not adequate and reliable coverage of the key parameters addressed in the corresponding test method, specifically: only 1000 polychromatic erythrocytes (PCE) per animal were scored for the incidence of micronuclei whereas 2000 and 4000 PCEs must be scored, according to OECD TG 1997 and OECD TG 2016, respectively.

ECHA concludes that the source study (ii), does not provide the information required by Annex VIII, Section 8.4.2., because it does not meet the requirements of Annex XI, Section 1.5, as set out above.

c) Conclusion on the grouping and read-across approach

For the reasons set out above, ECHA rejects the adaptation for in vitro cytogenicity in mammalian cells in the technical dossier based on Annex XI, Section 1.5.

In your comments to the draft decision you acknowledge ECHA's analysis on the rejection of the read-across approach. You indicate that you will consider whether such an approach can be improved or whether another adaptation may be used. ECHA highlights that any new information will be evaluated under Article 42 of REACH only after the deadline in the adopted decision has expired.

Test requested

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.

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).

3. 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 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. You have provided the following study record with the source substance 3 (see section 2 above).

- *In vitro* mammalian cell gene mutation assay (publication data: [redacted] equivalent to OECD TG 476, GLP not specified, your reliability score is 2), The purity of the test material is 99.51%. Results: negative with and without metabolic activation.

ECHA stresses that due to the different nature of each hazard property and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the property under consideration. ECHA could not identify individual arguments with regard to *in vitro* mammalian cell gene mutation. ECHA's analysis of your grouping and read-across approach presented above under 2 is therefore also applied to the property *in vitro* gene mutation in mammalian cells. ECHA concludes that based on the presented information in your read-across justification document, it is not possible to confirm that the registered substance and the source 3 substance would have similar genotoxicity properties.

Further, ECHA assessed the reliability and adequacy of the source study in accordance with the criteria of Annex XI, 1.5, provided above, under point 2.b) of this statement of reasons, and has the following observations: there is not adequate and reliable coverage of the key parameters addressed in the corresponding test method, specifically: no information for selecting the top concentration, no data on the number of colonies counted with and without the substance. From the tabulated data in the study report it is not clear if they represent the results from the module with or without metabolic activation.

ECHA concludes that the source study, does not provide the information required by Annex VIII, Section 8.4.3., because it does not meet the requirements of Annex XI, Section 1.5. as set out above under 2.

The adaptation of the standard information requirement *in vitro* gene mutation in mammalian cells in the technical dossier is based on the proposed grouping and read-across approach examined above. ECHA does not consider this approach to be a reliable basis to predict the property of the registered substance for the reasons set out above. Thus, the adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. Therefore, ECHA rejects the adaptation for *in vitro* gene mutation in mammalian cells in the technical dossier based on Annex XI, Section 1.5.

In your comments to the draft decision you acknowledge ECHA's analysis on the rejection of the read-across approach. You indicate that you will consider whether such an approach can be improved or whether another adaptation may be used ECHA highlights that any new information will be evaluated under Article 42 of REACH only after the deadline in the adopted decision has expired.

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.

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 1. and 2. have negative results.

4. 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 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.

You have not provided any study record of a screening for reproductive/developmental toxicity in the dossier that would meet the information requirement of Annex VIII, Section 8.7.1.

Instead, you sought to adapt this information requirement in accordance with Annex XI, section 3.2. (a) by providing the following justification:
"As required under Regulation (EC) 1907/2006, Annex XI, Section 3.2 (a) (i), the exposure assessment, covering all relevant exposure throughout the life cycle of the substance, demonstrated the absence of or no significant exposure in all the manufacturing scenarios and identified uses as defined in Annex VI section 3.5 of Regulation (EC) 1907/2006.
There is no study available for 2-(2-ethoxyethoxy) ethyl acetate (CAS 112-15-12) investigating the toxicity to reproduction. However a repeated dose toxicity study via the inhalation route with 2-(2-ethoxyethoxy) ethyl acetate is available resulting in a [redacted] *(Anonymous, 1992). As required under Regulation (EC) 1907/2006, Annex XI, 3.2 (a) (ii), DNELs were derived using this study, and applied to derive Risk Characterisation Ratios (RCRs).*
As required under Regulation (EC) 1907/2006, Annex XI, 3.2 (a) (iii), the RCRs were < 1, showing that exposures are always well below the derived DNEL.
The developed exposure scenarios demonstrating and documenting the fulfilment of the conditions mentioned above are provided in the Chemical Safety Report".

Section 3.2.(a) under Annex XI provides that testing in accordance with Annex IX and Annex X may be omitted, if the manufacturer or importer demonstrates and documents that all of the following conditions are fulfilled:

(i) the results of the exposure assessment covering all relevant exposures throughout the life cycle of the substance demonstrate the absence of or no significant exposure in all scenarios of the manufacture and all identified uses as referred to in Annex VI section 3.5;
(ii) a DNEL or a PNEC can be derived from results of available test data for the substance concerned taking full account of the increased uncertainty resulting from the omission of the information requirement, and that DNEL or PNEC is relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes;
(iii) the comparison of the derived DNEL or PNEC with the results of the exposure assessment shows that exposures are always well below the derived DNEL or PNEC

ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI, Section 3.2.(a), for the reasons stated below:

Firstly, ECHA considers that according to REACH Annex XI 3.2.(a)(i), you did not demonstrate *"absence of or no significant exposure in all scenarios".* ECHA notes that in the CSR there are many exposure scenarios with significant exposure. Particularly, with consumer exposure assessment detailed experimental measures of exposure would be required to demonstrate the absence of or no significant exposure.

Secondly, ECHA points out that according to Annex XI 3.2.(a)(ii), the DNEL derived from the available data must take into account the increased uncertainty resulting from the omission of the information requirement, i.e. the omission of the screening study for reproductive and developmental toxicity (Annex VIII, Section 8.7.1.) in the current case. ECHA notes that the DNEL value is derived from a repeated dose toxicity study via the inhalation route. ECHA considers that a DNEL derived from a sub-chronic toxicity (90-day) study, as sole basis, is not taking into account the uncertainty of the omission of the screening study. As also explained in the ECHA Guidance[3], a repeated-dose toxicity study "*showing no adverse effects on reproductive organs is **not** considered to provide sufficient information for a DNEL calculation for fertility or other reproductive effects*". Therefore, in absence of relevant and appropriate data for DNEL derivation, the criterion 3.2(a)(ii) is not met.

ECHA further notes that the derived DNEL is for systemic effects and it is based on NOAEC of [redacted] In the same inhalation study you also pointed out a NOEC of [redacted] based on the observed local effects in the lungs (increased weight and histopathological changes). In the study report you concluded that "*The changes were expected results of the particle load resulting from the high aerosol concentrations and represented a nonspecific response to a relatively innocuous aerosol*". ECHA notes that the observed adverse effects are treatment-related and have to be taken into account to derive a DNEL for local effects. ECHA concludes that the DNEL has not been correctly derived and therefore cannot be used in the context of Annex XI, section 3.2. (a, ii).

Finally, for professional workers you report a variety of RCR, from [redacted] up to [redacted]. For consumers you report RCR of [redacted]. The lowest value of RCR [redacted] is not considered well below the derived DNEL as required by Annex XI, section 3.2. (a, iii). Additionally, you report a number of higher values up to [redacted] for RCR.

In your comments to the draft decision you acknowledge ECHA's arguments for the rejection. ECHA understand that you acknowledge the need to perform the requested study.

Based on the analysis above, your adaptation of the information requirement according to Annex XI, section 3.2. (a) is rejected.

According to the test methods OECD TG 421/422, 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, with a vapour pressure of 0.013 kPa at 20°C, ECHA concludes that testing should be performed by the oral route.

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

[3] ECHA Guidance on information requirements and chemical safety assessment, Chapter R.8: Characterisations of dose [concentration]-response for human health (version 2.1, November 2012)

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 of the requested screening (OECD TG 421/422) and the developmental toxicity studies (OECD TG 414) 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."

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

A "pre-natal developmental toxicity study" (test method OECD TG 414) for a first species is a standard information requirement in Annex IX, Section 8.7.2. of the REACH Regulation.

You have not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2. Instead, you sought to adapt this information requirement in accordance with Annex XI, section 3.2. (a) by providing the identical justification as quoted above under 4.

As explained above under 4., your proposed adaptation based on Annex XI, Section 3.2 (a) is rejected since the condition of Annex XI 3.2 (a)(i) is not met. Moreover, for Annex XI 3.2 (a) (ii), ECHA considers that a DNEL derived from a sub-chronic toxicity (90-day) study, as sole basis, is not taking into account the uncertainty of the omission of the pre-natal developmental toxicity study. According to the ECHA Guidance document[4], a repeated-dose toxicity study "*showing no adverse effects on reproductive organs is not considered to provide sufficient information for a DNEL calculation for fertility or other reproductive effects*". Therefore, in absence of relevant and appropriate data for DNEL derivation, the criterion 3.2(a)(ii) is also not met.

In your comments to the draft decision you acknowledge ECHA's arguments for the rejection. ECHA understand that you acknowledge the need to perform the requested study.

Based on the analysis above, your adaptation of the information requirement according to Annex XI, section 3.2. (a) is rejected.

According to the test method 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.

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: OECD TG 414) in a first species (rat or rabbit) by the oral route.

6. Update of the technical dossier using the study "Devillers, 2003, C. dubia, 7 d, RL 3" as key study showing the highest concern for the endpoint of Long-term toxicity testing on invertebrates (Annex IX section 9.1.5.)

or

Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: Daphnia magna reproduction test, EU C.20./OECD TG 211) with the registered substance;

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. of the REACH Regulation.

You have sought to adapt this information requirement according to Annex IX, Section 9.1.5., column 2. You provided the following justification for the adaptation: "*The environmental exposure assessment for 2-(2-ethoxyethoxy)ethyl acetate (CAS 112-15-2) according to Annex XI, Section 3 of Regulation (EC) No 1907/2006 indicates no risk for the aquatic compartment (all RCR < 1; please refer to Chapter 9 and 10 of the Chemical Safety Report for detailed information). Thus, an additional long-term test with aquatic invertebrates is not deemed necessary.*"

Additionally you have provided the following study record for the standard information requirement of Annex IX, Section 9.1.5. Long-term toxicity testing on invertebrates: "[redacted]"
You have disregarded the study as you have considered it not reliable (reliability score 3) "*due to major methodological deficiencies*" and "*inconsistent results*". You further state in the endpoint summary that "*this result was not considered as reliable since a very wide confidence limit was determined (CI: 0.005 - 1.315 mg/L)*".

However, ECHA considers that disregarding this study for the CSA, and then adapting the information on long-term toxicity on invertebrates on the basis of that CSA, is not justified for the following reasons.

Firstly, ECHA notes that Annex I, Section 3.1.1 of the REACH Regulation requires for the CSA that the hazard identification is based on all available information. Furthermore, Section 3.1.5. requires that the study or studies giving rise to the highest concern shall normally be used to draw a conclusion and a robust study summary shall be prepared for that study or studies and included in the technical dossier. If a study giving rise to the highest concern is not used, then this shall be fully justified.

ECHA considers that you did not use the study giving rise to the highest concern to draw a conclusion for the hazard assessment. The study "[redacted]" which you disregard shows the highest concern for the aquatic environment as it resulted in a 7 day EC10 of 0.125 mg/L (confidence interval CI: 0.005 - 1.315 mg/L) while the acute

immobilisation study with *Daphnia magna* indicated toxicity only at limit concentration of 100 mg/L and no EC50 could be derived based on this study.

ECHA points out that your argument to disregard the study due to major methodological deficiencies is not substantiated with evidence. ECHA notes that there is no indication provided in the robust study summary or in the original publication that the study would have major methodological deficiencies as stated by you. In contrast ECHA notes that the study was conducted according to the Guideline AFNOR 2000 and fulfilled its validity criteria. You have not provided any evidence indicating that the design of the study had deficiencies or it did not fulfil the validity criteria set in AFNOR 2000.

You further argue that the large confidence intervals (CIs) derived for the EC10 value indicate the study is not reliable. ECHA notes that the study "[redacted]" is published in a peer reviewed journal and is available online. In the original publication it is stated that large CIs were indeed observed and that they were associated with lack of concentration–effect relationship. However the authors of the publication highlighted that similar observations on the lack of concentration–effect relationship have been made by other authors working on the developmental toxicity of ethylene glycol monomethyl ether and ethylene glycol monoethyl ether.

Therefore ECHA considers that large CIs seem to be more associated to the nature of the substances and their effects, and not to major methodological deficiencies as stated by you, taking into account that the study was conducted according to AFNOR 2000 and fulfilled its validity criteria. However ECHA agrees that the large CIs do indicate certain degree of uncertainty around the exact effect value reported.

ECHA further considers that the provided study can be used to fulfil this information requirement. According to ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, chronic tests with crustacea should include at least 3 broods produced during the exposure period and Ceriodaphnia dubia produces 3 broods within 7 d. ECHA therefore considers that the provided 7-d Ceriodaphnia study can be used to fulfil this information requirement.

In conclusion, ECHA considers that your argument to disregard the study due to major methodological deficiencies is not supported by evidence and the study can be considered reliable.

Consequently, by disregarding this study the hazard identification is not based on all available information and the study giving rise to the highest concern has not been used to draw a conclusion on the hazards of the registered substance. Therefore your CSA does not comply with Annex I, Section 3 of the REACH Regulation and consequently does not allow to adapt this information requirement.

Secondly, ECHA notes that column 2 of Annex IX, Section 9.1 of the REACH Regulation indicates that long-term toxicity testing shall be considered if the CSA indicates a need to investigate further the effects on aquatic organisms.

ECHA points out that the need to consider long-term testing in the CSA is triggered not only by a quantitative assessment, where the RCR>1, but may also be triggered by results from a qualitative assessment as described in ECHA *Guidance on information requirements and*

chemical safety assessment (version 4.0, June 2017) Chapter R7.b (Section R.7.8.4.3). The qualitative assessment may indicate that a possible risk should be confirmed/rejected when there is information on a specific mode of action and unexpected sensitivity of a group of organisms to the substance under investigation. In such cases the acute data has been shown to have only limited predictive value for long-term effects and the risks to aquatic ecosystem may not be controlled (ECHA Guidance Chapter R.7b, Ahlers et al. 2006[4]). In particular, a factor of 10 is considered to cover the uncertainty when extrapolating the chronic toxicity from acute toxicity data for neutral organic substances, within the Assessment Factor (AF) method of deriving the PNEC for risk assessment. However it is considered that delayed toxic effects such as those affecting reproduction cannot be predicted at all on the basis of acute tests (OECD 1992[5]).

In your adaptation to this information requirement you argue that there is "*no risk for the aquatic compartment (all RCR < 1...* ". However, ECHA considers that long-term toxicity testing for the registered substance is triggered by a qualitative assessment. In particular, the disregarded study "[redacted]" reports sublethal effects on reproduction in long-term exposure (7-d including 3 broods) with an EC10 of 0.125 mg/L (confidence interval CI 0.005–1.315 mg/L) while the submitted short-term toxicity study for aquatic invertebrates indicates an EC50 of >100mg/L. Based on these results the acute to chronic ratio would be 800 (CI 20 0000 - 76). This indicates a specific mode of action where the standard factor of 10 would not cover the extrapolation from acute to chronic effects for the registered substance within the CIs identified from the existing chronic study. Therefore the current quantitative risk assessment using the standard AF method may not be protective for the long-term hazards of the substance.

Consequently, ECHA considers that the CSA indicates a need to consider the long-term effects on aquatic organisms to ensure that the risks of the substance are adequately controlled.

In conclusion, your adaptation of the information requirement based on the CSA cannot be accepted and it is necessary to provide reliable information on long-term toxicity to aquatic invertebrates in your dossier.

In your comments to the draft decision, you acknowledge ECHA's arguments for the rejection of this endpoint, and you indicated that you intend to improve the robust study summary as requested in this decision.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to update the technical dossier and the Chemical Safety Report using the study showing the highest concern "[redacted]" as key study for the endpoint of Long-term toxicity testing on invertebrates (Annex IX section 9.1.5.).

Alternatively, if you consider that the study result is not reliable with regards to exact effect value and the uncertainty around the effect value, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the

[4] Ahlers et al. 2006: Acute to chronic ratios in aquatic toxicity - variation across trophic levels and relationship with chemical structure. Environ. Toxicol. Chem. 25, pp 2937-2945

[5] OECD 1992. Report of the OECD Workshop on the extrapolation of laboratory aquatic toxicity data on the real environment. Organisation for Economic Cooperation and Development (OECD), OECD Environment Monographs No 59, Paris.

registered substance subject to the present decision: Daphnia magna reproduction test (test method: EU C.20./OECD TG 211) with the registered substance.

7. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.)

"Long-term toxicity testing on fish" is a standard information requirement in Annex IX, Section 9.1.6. of the REACH Regulation. Adequate information on Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.), or Fish, short-term toxicity test on embryo and sac-fry stages (Annex IX, 9.1.6.2.), or Fish, juvenile growth test (Annex IX, 9.1.6.3.) 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 IX, Section 9.1.6., column 2. You provided the following justification for the adaptation: "*In accordance with Annex IX, column 2 of Regulation (EC) No 1907/2006, long-term toxicity testing to fish does not need to be conducted as the Chemical Safety Assessment does not indicate a need for further investigations. The environmental exposure assessment for 2-(2-ethoxyethoxy)ethyl acetate (CAS 112-15-2) according to Annex XI, Section 3 of Regulation (EC) No 1907/2006 indicates no risk for the aquatic compartment (all RCR < 1; please refer to Chapter 9 and 10 of the Chemical Safety Report for detailed information). Thus, a long-term test with fish is not deemed necessary.*"

For the same reasons as explained above in the request 6 of this decision, your adaptation of the information requirement cannot be accepted.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) fish early-life stage (FELS) toxicity test (test method OECD TG 210), fish short-term toxicity test on embryo and sac-fry stages (test method EU C.15. / OECD TG 212) and fish juvenile growth test (test method EU C.14. / OECD TG 215) can be performed to cover the standard information requirement of Annex IX, Section 9.1.6.

However, the FELS toxicity test according to OECD TG 210 is more sensitive than the fish, short-term toxicity test on embryo and sac-fry stages (test method EU C.15 / OECD TG 212), or the fish, juvenile growth test (test method EU C.14. / OECD TG 215), as it covers several life stages of the fish from the newly fertilized egg, through hatch to early stages of growth (see ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), *Chapter R7b, Section R.7.8.4.1.*

Moreover, the FELS toxicity test is preferable for examining the potential toxic effects of substances which are expected to cause effects over a longer exposure period, or which require a longer exposure period of time to reach steady state (ECHA *Guidance Chapter R7b,* version 4.0, June 2017).

In your comments to the draft decision, you acknowledge ECHA's arguments for the rejection of the provided information, and the requirement to consider classification based on the existing Long-term toxicity study on aquatic invertebrates. You state that if classification and labelling is needed based on the existing long-term invertebrate study, "there will be, as a result, adequate safeguarding of the aquatic environment". However, ECHA notes that while classification is part of CSA referred to in column 2 of Annex IX Section 9.1.6 , it is not itself an acceptable waiver for the endpoint Long-term toxicity study

on fish. Chemical Safety Assessment includes hazard assessment (PNEC derivation and classification) and PBT assessment.

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: Fish, early-life stage (FELS) toxicity test (test method: OECD TG 210).

Notes for your consideration for requests 6-7

ECHA notes that it is not possible to determine the interspecies variation in sensitivity to the registered substance which would allow application of the Integrated testing strategy (ITS) outlined in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b (Section R.7.8.5 including Figure R.7.8-4). Firstly, while short-term studies on the three trophic levels are submitted, the results from the short-term studies on *Daphnia magna* and algae could not be used to derive an accurate EC50/LC50 because of low lethal toxicity up to limit concentration of 100 mg/L. Secondly, the existing long-term toxicity study on aquatic invertebrates ([redacted]) has indicated a potential specific mode of action inducing sublethal effects. In the absence of chronic studies on fish, the relative sensitivity between the trophic levels cannot be determined with respect of sublethal effects.

Therefore, the ITS is not applicable in this case and the long-term studies on both invertebrates and fish are requested to be conducted.

8. Classification and labelling (Annex VI, Section 4.): Apply classification and labelling on the registered substance for long-term aquatic hazard or provide a justification for not classifying.

Pursuant to Article 10(a)(iv) of the REACH Regulation your technical dossier shall contain information on classification and labelling of the substance as specified in Annex VI, Section 4 of the REACH Regulation in conjunction with Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures (CLP Regulation).

Annex VI, section 4.1. clarifies that the hazard classification of the substance shall result from the application of Titles I and II of the CLP Regulation. In addition, for each entry, the scientifically justified reasons why no classification is given for a hazard class or differentiation of a hazard class should be provided. According to Article 5(1) of Title I of the CLP Regulation, a substance shall be classified on the basis of available information.

Furthermore, the technical dossier must include the resulting hazard label for the substance in line with Title III of the CLP Regulation (Annex VI, section 4.2 of the REACH Regulation).

According to the CLP Regulation, Annex I, Section 4.1, classification of the substance as hazardous to the aquatic environment recognises that the intrinsic hazard to aquatic organisms is represented by both the acute and long-term hazard of a substance. For the long-term hazard (Table 4.1.0 (b)), separate hazard categories are defined representing a gradation in the level of hazard identified for (i) Non-rapidly degradable substances for which there are adequate chronic toxicity data available, (ii) Rapidly degradable substances for which there are adequate chronic toxicity data available, and (iii) Substances for which

adequate chronic toxicity data are not available. The lowest of the available toxicity values between and within the different trophic levels (fish, crustacean, algae/aquatic plants) shall normally be used to define the appropriate hazard category(ies).

You have reported a degradation of 101% in 28 days in a ready biodegradability test performed according to OECD Guideline 301 C (Ready Biodegradability: Modified MITI Test (I)). This indicates a rapid degradation of the registered substance based on the criteria set in the Annex I Section 4.1.2.9 of the CLP Regulation describing that a substance is considered likely to biodegrade "rapidly" in the aquatic environment if it passes the screening test (i.e. 60 % degradation based on oxygen depletion fulfilling the 10-d window).

According to Table 4.1.0 (b)(ii), for a rapidly degradable substance for which there are adequate chronic toxicity data available, Category Chronic 3 is indicated when Chronic NOEC or EC50 for fish, crustacean or algae/aquatic plants ≤1 mg/L.

You provided a chronic study on *Ceriodaphnia dubia* "[redacted]) but disregard the study and do not use it in your Chemical Safety Assessment (CSA). For the reasons described in the request 6 ECHA considers that you have not provided evidence to indicate that this study would be unreliable.

ECHA notes that the provided study ("[redacted]") indicates that toxicity may occur in concentrations lower than 1 mg/L, indicating that classification of the substance should be considered. The reported EC10 (*C. dubia*, 7-d including 3 broods, reproduction) is 0.125 mg/L. Despite the observed toxicity in *C. dubia* study you have not self-classified the substance for long-term aquatic hazards. Furthermore, ECHA observes that the dossier does not contain any justification for non-classification, but only the statement: "conclusive but not sufficient for classification."

In your comments to the draft decision, you acknowledged ECHA's arguments and indicated that you intended to update the dossier accordingly. ECHA understands that you agree to the draft decision.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to classify and label the registered substance taking into account the information requested in this decision (requests 6-7). In the alternative, you are requested to provide the scientifically justified reasons why no such classification is given.

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 20 July 2018.

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 within 30 days of the notification.

ECHA took into account your comments and did not amend the request(s).

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.