EUROPEAN CHEMICALS AGENCY

Helsinki, 15 December 2016

Addressee: [redacted]

Decision number: CCH-D-2114350583-50-01/F
Substance name: ETHYLENE DI(ACETATE)
EC number: 203-881-1
CAS number: 111-55-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 05.04.2013
Registered tonnage band: 100-1000T

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 mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance;**

2. **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;**

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

4. **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 of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **24 June 2019**. 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. Advice and further observations are provided in Appendix 3.

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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, shall 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 Kevin Pollard, Head of Unit, Evaluation E1

[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

0. Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "provided that the conditions set out in Annex XI are met".

Annex XI, Section 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation.

In the registration, you have adapted the standard information requirements for; e.g.,

- *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

by applying a read-across adaptation following REACH Annex XI, Section 1.5. to structurally different substances. This read-across adaptation is addressed within this section of the decision.

You have further adapated the standard information requirement for

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

by applying, *inter alia*, a read-across adaptation following REACH Annex XI, Section 1.5. to an analogue substance and an exposure-based adaptation following REACH Annex XI, Section 3.2.(a). The read-across adaptation is addressed within this section of the decision, whereas the exposure-based adaptation is addressed below under section "3.".

The following analysis presents your justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and an property-specific context.

0.1 Description of your read-across approach

You suggest that the general rules for grouping and read-across approach laid down in Annex XI, Section 1.5. of the REACH Regulation apply to aquatic ecotoxicology and the health hazard assessment of the target (registered) substance ethylene di(acetate) (CAS 111-55-7; EC 203-881-1). Furthermore, you conclude that the analogue substances listed in the read-across support document can be used to close data-gaps in the aquatic ecotoxicology as well as in the health hazard assessment of the target substance as the target and source substances share the following properties:

(i) Common functional groups
(ii) Common precursors and likelihood of common breakdown products
(iii) Similar physico-chemical properties
(iv) Common properties for environmental fate & eco-toxicological profile of the category members
(v) Similar metabolic pathways
(vi) Common levels and mode of human health related effects

The analogue substances included in the read-across approach are

- 2,2'-[ethane-1,2-diylbis(oxy)]bisethyldiacetate (source [1]; mono constituent; CAS 111-21-7; 203-846-0) used as source substance for some environmental endpoints (biodegradation and toxicity to microorganisms);
- Propane-1,2-diyldiacetate (source [2]; mono constituent; CAS 623-84-7; EC 210-817-6) used as source substance for some human health endpoints (acute dermal and inhalation toxicity, eye irritation, skin sensitisation, repeated dose toxicity, *in vitro* mammalian gene mutation test, pre-natal developmental toxicity).

Furthermore, you make the following statement:

"According to the general rules for grouping of substances and read-across approach laid down in Annex XI, Item 1.5, of Regulation (EC) No. 1907/2006, substances may be considered as a group provided that their physicochemical, toxicological and ecotoxicological and environmental fate properties are likely to be similar or follow a regular pattern as a result of structural similarity. The substances within the analogue approach (listed in Table 1) are considered to apply to these general rules and the similarity is justified on basis of scope of variability and overlapping of composition, representative molecular structure, physico-chemical properties, tox-, ecotoxicological profiles and supported by various (Q)SAR methods. There is convincing evidence that these chemicals lie in the overall common profile of this analogue approach."

ECHA regards this as the hypothesis under which you make predictions.

0.2 Information you submitted to support of the grouping and read-across approach

You have provided a read-across justification as a separate attachment in IUCLID section 13.

You have provided the following study records in the IUCLID dossier with regard to human health endpoints:

- Sub-acute dermal toxicity study (28 days) in rats with the analogue substance propane-1,2-diyldiacetate (CAS No 623-84-7; [redacted], 1987), NOEL > 1000 mg/kg bw/day;
- *In vitro* mammalian cell gene mutation test with the analogue substance propane-1,2-diyldiacetate (CAS No 623-84-7; [redacted], 2011), negative with and without metabolic activation;

- Prenatal Developmental Toxicity Study in rabbit with the analogue substance propane-1,2-diyldiacetate (CAS No 623-84-7; [redacted], 1989), $NOAEL_{maternal/developmental}$ 1058 mg/kg bw/day;

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

With regard to the proposed prediction for human health endpoints ECHA has the following observations:

(i) Common functional groups

You indicate that "*The target and the source substances are characterized by ester bond(s) between an alcohol (ethylene glycol, triethylene glycol, propylene glycol) and acetic acid.*"

ECHA observes that the registered substance is an ethylene glycol ester, whereas the source substance used for read-across purposes for human health endpoints is a propylene glycol ester. ECHA notes that the structural differences of source and target substances may lead to differences in toxicokinetic and toxicity profile as discussed under iii) and iv). ECHA consideres that there is a failure to satisfy the requirement of Annex XI, 1.5 with respect to common functional groups.

(ii) Similar physico-chemical properties

You state that "*For the purpose of read-across of (eco)toxicity data, the most relevant physico-chemical parameter are physical state (appearance), vapour pressure, octanol/water partition coefficient and water solubility. All substances have in common, a high water solubility (≥171.1 g/L), a low log Pow (0.03/0.14 – 0.82) and a vapour pressure between 0.04 – 29.86 Pa at 20 °C).*"

ECHA notes that the fact that physico-chemical parameters do not show significant differences may support the similar toxicokinetic and toxicity profile, but cannot be used alone to justify a prediction of properties related to human health in absence of other supporting information as discussed under iii) and iv).

(iii) Similar metabolic pathways

You state that "*Esters of acetic acid with an alcohol are anticipated to be initially metabolised via enzymatic hydrolysis to the corresponding free acids and the free glycol alcohols such as ethylene glycol, and propylene glycol. The hydrolysis represents the first chemical step in the absorption, distribution, metabolism and excretion (ADME) pathways likely to be similarly followed by all glycol esters. The alcohol components, ethylene glycol and propylene glycol are rapidly absorbed from the gastrointestinal tract and subsequently undergo rapid biotransformation in liver and kidney or are excreted unmetabolised via the urine. Ethylene glycol is metabolised by alcohol dehydrogenase to glycoaldehyde, which is then further oxidised successively to glycolic acid, glyoxylic acid, oxalic acids by mitochondrial aldehyde dehydrogenase and cytosolic aldehyde oxidase.*

Propylene glycol is metabolised in liver by alcohol dehydrogenase to lactic acid and pyruvic acid which are endogenous substances naturally occurring in mammals. Acetic acid and the respective acetate ion are normally-occurring metabolites in catabolism or in anabolic synthesis, e.g. in the formation of glycogen, cholesterol synthesis and degradation of fatty acids."

ECHA acknowledges that one common metabolite of target and source substances is acetic acid. However, ECHA notes the differences in other metabolites. More specifically, you indicate that the other main metabolite of the registered substance is ethylene glycol, which is "*oxidised successively to glycolic acid, glyoxylic acid, oxalic acids*". However, the main metabolite of the source substance used for human health endpoints is propylene glycol "*which is metabolised in liver by alcohol dehydrogenase to lactic acid and pyruvic acid*". ECHA notes the structural differences in the metabolites of target and source substance and their different metabolism. You did not provide any information and supporting evidence on the toxicity of ethylene glycol and propylene glycol to support your read-across approach.

ECHA further notes that information on hydrolysis of the parent compounds is an important aspect to be considered. In the dossier you have provided information on an *in vitro* hydrolysis test in simulated intestinal fluid at pH 7.5 (37°C) performed with the registered substance. The half-life was determined with approximately 26 hours. ECHA considers that such hydrolysis rate suggests that absorption and systemic exposure to the unchanged parent compound cannot be excluded. ECHA further notes that information on hydrolysis of the registered substance under acidic conditions has not been provided. In addition, no information on the hydrolysis of the source substances, has been provided.

ECHA concludes that you did not address in sufficient detail the hydrolysis of the source and target substances. Furthermore, you have not provided information on how the metabolic differences may impact the toxicity of the substances and thus affect the possibility to predict the properties of the registered substance from the data of the analogue substance. In the absence of such information ECHA is unable to conclude on the prediction of the properties of the registered substance from the data obtained with the source substances. Therefore, ECHA consideres that there is a failure to satisfy the requirement of Annex XI, 1.5 with respect to the common precursors and/or the likelyhood of common breakdown products via physical and biological processes, which result in structurally similar chemicals.

(iv) Common properties for environmental fate & eco-toxicological profile of the category members

ECHA notes that this decision addresses only read-across related to human health endpoints.

(v) Similar metabolic pathways and common levels and mode of human health related effects

You state that "*The toxicological properties show that the target and source substances have similar toxicokinetic behaviour (hydrolysis of the ester bond before absorption followed by absorption and metabolism or excretion of the breakdown products). The members of the analogue approach showed a low acute oral, dermal and inhalative toxicity, no skin and eye irritation and no sensitisation properties.*
No repeated dose toxicity was observed for the target and source substance and no mutagenic or clastogenic properties have been shown. Furthermore, the target and source substances are not classified for reproduction toxicity and developmental toxicity."

ECHA considers the following:

Mutagenicity

ECHA notes that you have provided information on genotoxicity of the target and source substances. You state the following: "*The studies with Ethylene diacetate (CAS 111-55-7) investigating genetic mutations in bacteria in-vitro and cytogenicity in mammalian cells in-vitro provided negative results. In addition, no mutagenicity in mammalian cells in-vitro was observed with the structurally related analogue substance Propane-1,2-diyl diacetate (CAS 623-84-7). Therefore, the available data do not provide any indications for a potential genetic toxicity of Ethylene diacetate (CAS 111-55-7).*"

ECHA notes that you provided a test with the source substance [2] Propane-1,2-diyldiacetate for *in vitro* mammalian cell gene mutation test, but no appropriate information on gene mutation in mammalian cells for the target (registered) substance. Considering the differences in structure of target and source substance and the toxicokinetic differences, especially the different metabolites of ethylene and propylene glycol, as described under (i), (ii), and (iii), ECHA considers that you have not explained how and why the outcome of the *in vitro* mammalian cell gene mutation test with source substance [2] can be used to accurately predict the outcome of the same test for the target (registered) substance. Therefore, ECHA consideres that there is a failure to satisfy the requirement of Annex XI, 1.5 that the proposed analogue substance can be used to predict properties of the registered substance.

Repeated dose toxicity

You have provided a dermal repeated dose toxicity study with the source substance [2] Propane-1,2-diyldiacetate in the registration dossier and state that "*Based on the read-across data, no hazard was identified for (subacute) repeated dose toxicity by the dermal route.*" Furthermore, you state that "*No repeated dose toxicity was observed for the target and source substance.*"

Firstly, ECHA notes that no reliable repeated dose toxicity data with the registered substance has been provided in the registration dossier. Therefore ECHA considers that there is no reliable basis whereby the source substance can be used to predict properties for the registered substance.

Secondly, ECHA notes that due to the assumed different metabolites as described under iii), the systemic toxicity profiles of the target and source substances have not been demonstrated to be similar and that further prediction of the sub-chronic toxicity of the registered substance is not possible. Therefore ECHA consideres that there is a failure to satisfy the requirement of Annex XI, 1.5 that the proposed analogue substance can be used to predict properties of the registered substance.

Developmental toxicity

You have provided a developmental toxicity study with the source substance [2] Propane-1,2-diyldiacetate in the registration dossier and state that "*The study from Propane- 1,2-diyl diacetate did not show treatment-related effects up to the highest tested dose level. Thus, no hazard for developmental toxicity was identified and a NOAEL for developmental toxicity is considered to be above the highest dose level (1000 mg/kg bw/day (m, f)).*"

Firstly, ECHA notes that no information on developmental toxicity with the registered substance has been provided in the registration dossier. Following the considerations above, ECHA considers your statement about the unidentified developmental toxic hazard and NOAEL for developmental toxicity inadequate in absence of further supporting information of the target and source substances.

Secondly, ECHA notes that due to the assumed different metabolites, as described under iii), the systemic toxicity profiles of the target and source substances have not been demonstrated to be similar and that further prediction of the developmental toxicity of the registered substance is not possible based on the current information from the analogue.

ECHA concludes that the presented evidence does not support a similar or regular pattern of toxicity as a result of structural similarity. Therefore, ECHA consideres that there is a failure to satisfy the requirement of Annex XI, 1.5. that the proposed analogue substance(s) can be used to predict properties of the registered substance.

ECHA further notes that for the endpoints on repeated dose toxicity and reproductive toxicity, you provided an exposure-based adaptation. These adaptations are addressed below under the respective endpoints.

0.4 Conclusion on your read-across approach

ECHA concludes that in view of the issues listed above it has not been demonstrated that the source and target substances have the same properties or follow a similar pattern with regard to studies on *in vitro* mammalian cell gene mutation, sub-chronic toxicity (90-day) and developmental toxicity. Hence you have failed to meet the requirement of Annex XI, Section 1.5. that human health effects may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach).

Pursuant to Article 41(1) of the REACH Regulation, ECHA concludes that the adaptation of the standard information requirement for the endpoint *in vitro* mammalian cell gene mutation, sub-chronic toxicity study (90-day) and developmental toxicity in the technical dossier based on the proposed read-across approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. Therefore, ECHA rejects the adaptations in the technical dossier that are based on Annex XI, 1.5.

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

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

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.

ECHA notes that the registration dossier contains negative results for both these information requirements. More specifically, negative results were observed in a bacterial reverse mutation assay (OECD TG 471) and in an *in vitro* mammalian chromosome aberration test (OECD TG 473) on the registered substance. Therefore, adequate information *on in vitro* gene mutation in mammalian cells 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 records for an *in vitro* mammalian cell gene mutation study (OECD TG 476) with the analogue substance Propane-1,2-diyldiacetate (CAS 623-84-7). However, as explained above in section 0 of this Appendix (Reasons), 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 comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you agree to perform an *in vitro* mammalian cell gene mutation test (OECD TG 476 or 490).

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).

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

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

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 provided the following information with respect to repeated dose toxicity:

- Oral: disregarded sub-chronic toxicity study (Kersten et al. 1939) because "*Only few details given in a publication*"
- Inhalation: adaptation according to Annex XI, Section 3.2.(a)
- Dermal: key study "Assessment of Subacute Dermal Toxicity of [trade name] in the rat: 28-day study" according to OECD TG 410 and GLP, [redacted] 1987 (study report) with the analogue substance propane-1,2-diyldiacetate (CAS 623-84-7)

Firstly, ECHA acknowledges that you have disregarded the oral sub-acute toxicity study (Kersten et al., 1939).

Secondly, 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 a repeated dose dermal toxicity: 21/28-Day Study (OECD TG 410) with the analogue substance propane-1,2-diyldiacetate (CAS 623-84-7). However, as explained above in section 0 of this Appendix (Reasons), your adaptation of the information requirement is rejected.

Thirdly, you have sought to adapt this information requirement according to Annex XI, Section 3.2.(a). You have provided the following justification: *"In accordance with Annex XI, Section 3 of Regulation (EC) 1907/2006, testing in accordance with Annex IX and Annex X may be omitted, based on the exposure scenario(s) developed in the Chemical Safety Report, provided that any one of the criteria set out in Annex XI Section 3.2 is met. [...] There is no 90-day study available for Ethylene diacetate (CAS 111-55-7) investigating repeated dose toxicity by any route. However a 28-day repeated dose toxicity study via the dermal route with Propane-1,2-diyl diacetate (CAS 623-84-7) is available, resulting in a NOAEL of > 1000 mg/kg bw/day ([redacted], 1987). 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."

For the following reasons your adaptation cannot be accepted:

The adaptation should meet the general rule for adaptation of Annex XI, Section 3.2 where you need specifically to demonstrate that the conditions, in this case, of Section (a) are fulfilled. In particular, Annex XI, Section 3.2.(a)(i) requires you to demonstrate and document that "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."
Annex XI, 3.2.(a)(iii) requires that a comparison of the derived DNEL with the results of the the exposure assessment shows that exposures are always well below the derived DNEL.

In your Chemical Safety Report you present 145 Exposure Scenarios, containing many contributing exposure scenarios relating to industrial, professional and consumer uses. Many of the contributing scenarios generate risk characterisation ratios over 0.6 and require a combination of risk management measures to be introduced in the modelling to achieve this level. Predicted risk characterisation ratios as high as 0.6 are not considered demonstration of "absence of or no significant exposure" or "well below the the derived DNEL". In fact, they indicate presence of significant exposure.

Further, you have predicted exposures for PROC 7 (industrial spraying using the pure substance) using the Easy TRA tool, which incorporates the ECETOC TRA model. The ECETOC TRA tool does not provide reliable estimates of exposure for liquid aerosols arising from industrial spraying and it is outside the domain of applicability of the tool. The estimates of inhalation exposure at industrial spraying are unreliable. ECETOC's own guidance (Technical Report 114) states: *"Although exposures to aerosol mists might be expected to be associated with certain uses which are open and associated with the release of significant amounts of energy(e.g. spraying, machining etc.), the TRA does not address such exposures."*

In addition, ECHA notes that your adaptation does not meet Annex XI, Section 3.2.(a)(ii). You indicate that "*DNELs were derived using this study (a 28-day repeated dose toxicity study via the dermal route with Propane-1,2-diyl diacetate (CAS 623-84-7) is available), and applied to derive Risk Characterisation Ratios (RCRs)".* You have derived DNELs using a 28-day repeated dose toxicity study which is not considered appropriate according to the footnote of Annex XI, Section 3.2.(ii). Furthermore, the study was performed with an analogue substance and your read-across approach is rejected (see Section "0." above).

Because of the deficiencies highlighted above, ECHA considers that the adaptation of the information requirement you have provided does not meet any of the conditions set in Annex XI, section 3.2, and your adaptation of the information requirement is therefore 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 4.1, October 2015) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. Though the information indicates that human exposure to the registered substance by the inhalation route is likely, in the absence of any repeated does toxicity study by the oral route ECHA considers this default route as most appropriate. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you propose to first conduct a combined repeated dose toxicity study with reproductive/developmental toxicity screening test and based on its outcome to re-evaluate the appropriateness of a read-across approach to propane-1,2-diyldiacetate (EC 210-817-6) according to Annex XI, Section 1.5. and to investigate the possibility for exposure based waiving according to Annex XI, Section 3. ECHA acknowledges your strategy, but notes that according to the footnote of Annex XI, Section 3.2.(a)(ii), a DNEL derived from a 28 day repeated dose toxicity study is not considered appropriate to omit a sub-chronic toxicity study (90-day). The repeated dose combined reproductive/developmental toxicity screening test addresses eaqually only sub-acute repeated dose toxicity (28 days) and therefore the same footnote applies.

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

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.

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

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

"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 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.

You have provided a study record for a publication "*Experimental Studies on Toxicity of Ethylene Glycol Alkyl Ethers in Japan*" (Nagano et al., 1984) which you flagged as "*weight of evidence*" and which you assigned as reliability 4 (not assignable) because "*Only few details given in a publication*". ECHA acknowledges that this study investigated the effect of the registered substance on testis of male mice but does not provide the information as investigated in a screening test for reproductive/developmental toxicity.

You have further sought to adapt this information requirement according to Annex XI, Section 3.2.(a) by providing the same justification as cited above in section 2 of this Appendix (Reasons). It is explained in that section above why your adaptation does not meet the general rules for adaptation of Annex XI; Section 3.2.(a) and therefore 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.

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 4.1, October 2015) R.7a, chapter 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: 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.

In your comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you agree to perform a combined repeated dose toxicity study with reproductive/ developmental toxicity screening test (OECD TG 422).

Notes for your consideration

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 4.1, October 2015).

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

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

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 provided a study record for a publication "*Developmental Toxicity and Structure/Activity Correlates of Glycols and Glycol Ethers*" (Johnson 1984) which you flagged as "supporting study" and which you assigned as reliability 4 (not assignable). However, this study does not provide the information required by Annex IX, Section 8.7.2., because it is an *in vitro* short-term screening test performed in adult polyps of the fresh water coelenterate Hydra attenuate that cannot provide the required information of a pre-natal developmental toxicity study (OECD 414). This test method requires investigation of substance-related effects on the embryo and foetus (like skeletal and visceral examination) in a mammalian species (rat and/or rabbit).

You have sought further to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a prenatal developmental toxicity study (OECD TG 414) with the analogue substance propane-1,2-diyldiacetate (CAS 623-84-7). However, as explained above in section 0 of this Appendix (Reasons), 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.

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 4.1, October 2015) R.7a, chapter 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 comment(s) on the draft decision according to Article 50(1) of the REACH Regulation you agree to first conduct a combined repeated dose toxicity study with reproductive/developmental toxicity screening test and based on its outcome to re-evaluate the appropriateness of a read-across approach to propane-1,2-diyldiacetate (EC 210-817-6) according to Annex XI, Section 1.5. ECHA acknowledges your proposed strategy without taking position at this point.

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.

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 16 June 2016.

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 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 request(s) in this decision, or to fulfil otherwise the information requirement(s) 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 test(s) 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 test(s) 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 test(s) must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.