EUROPEAN CHEMICALS AGENCY

Helsinki, 30 November 2016

Addressee: [redacted]

Decision number: CCH-D-2114348443-50-01/F
Substance name: Diethoxymethane
EC number: 207-330-6
CAS number: 462-95-3
Registration number: [redacted]
Submission number: [redacted]
Submission date: 23.11.2012
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 cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2, test method: EU B.10/OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2, test method: OECD TG 487) with the registered substance;**

2. **Transgenic rodent somatic and germ cell gene mutation assays (Annex IX, Section 8.4, column 2; test method: EU B.58/OECD TG 488) in transgenic mice or rats, inhalation route on the following tissues: liver and lung with the registered substance;**

   OR

   In vivo mammalian alkaline comet assay (Annex IX, Section 8.4, column 2; test method: OECD TG 489) in rats, inhalation route, on the following tissues: liver, and lung with the registered substance;

3. **Sub-chronic toxicity study (90-day), inhalation route (Annex IX, Section 8.6.2; test method: OECD TG 413) in rats with the registered substance;**

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

5. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2; test method: EU B.31/OECD TG 414) in a first species (rats or rabbits), oral route with the registered substance;**

6. **Robust study summary for key study, Ewell WS, Gorsuch JW, Kringle RO (1986), Simultaneous Evaluation of the Acute Effects of Chemicals on Seven Aquatic Species (Environmental Toxicology and Chemistry, Vol. 5, pp 831-840, 1986) (Annex VII, Section 9.1.1. in conjunction with Annex I, Section 3.1.5);**

7. **Robust study summary for key study, Eastman (1994), Diethoxymethane MSDS (Annex VIII, Section 9.1.3. in conjunction with Annex I, Section 3.1.5);**

8. **Simulation testing on ultimate degradation in surface water (Annex IX, Section 9.2.1.2; test method: Aerobic mineralisation in surface water – simulation biodegradation test, EU C.25/OECD TG 309) at a temperature of 12 °C with the registered substance;**

9. **Identification of degradation products (Annex IX, 9.2.3.) using an appropriate and suitable test method, as explained in section 8 below.**

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 **8 June 2020**. 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.

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

You have proposed to cover the standard information requirements for Diethoxymethane (hereafter referred to as "ethylal") for:

- *in vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2);*
- *in vivo somatic cell genotoxicity (Annex IX, Section 8.4. column 2);*
- *sub-chronic toxicity study (90-day; Annex IX, Section 8.6.2.)* and
- *pre-natal developmental toxicity study (Annex IX, Section 8.7.2.).*

by applying a read-across adaptation following REACH Annex XI, Section 1.5.

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, 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. 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 endpoint-specific context.

A. Description of the grouping and read-across approach proposed by the Registrant

You have provided a read-across approach which is based on grouping of selected acetal-moiety containing substances i.e. methylal, ethylal, butylal, 1,3-dioxolane, 2,5,7,10-tetraoxaundecane and 2-ethylhexylal. Depending on the availability of the relevant experimental studies, the substances were employed either as source or target substances. The outcome of the studies with the source substances were used to predict the genotoxic, the sub-chronic toxicity and the pre-natal developmental toxicity properties of the target substance(s). In the current decision ECHA limits the analysis to the predictions proposed for ethylal (i.e. the target/ registered substance).

In order to determine the genotoxic properties of ethylal you used an *in vitro* cytogenicity study in mammalian cells and an *in vivo* somatic cell genotoxicity study on the source substance methylal (CAS no 109-87-5).

In your dossier, Submission number: [redacted], you proposed a read-across strategy as described below.

In order to determine the repeated dose toxicity of the target substance you used studies conducted on the source substances methylal and 1,3-dioxolane (CAS no 646-06-0; hereafter referred to as "dioxolane").

In order to determine the pre-natal developmental toxicity of the target substance you used a study conducted on the source substance methylal.

ECHA understands that the grouping approach you applied is based on the similarity in the chemical structure of the above mentioned substances, namely that all substances contain an acetal moiety as a functional group.

For the properties investigated in the *in vitro* cytogenicity study in mammalian cells and in the *in vivo* somatic cell genotoxicity you have provided the following justification:

"The read-across analysis was performed for the genotoxicity super endpoint, which include three endpoints (mouse lymphoma assay, mammalian chromosome aberration test (in vitro), micronucleus test or UDS assay), that were treated with the same reasoning in terms of mechanism action and for which the read-across follow a similar justification. In the current study, methylal and dioxolane were selected by the commissioner as source chemicals or analogs, to predict the same endpoints for the target chemicals, i.e. ethylal [...] The suggested source chemicals, i.e. methylal and dioxolane, can be considered sufficient similar in relation to the genotoxicity super endpoint to the target chemicals, i.e. ethylal, [...] to apply the read-across approach. Their structural similarity is also supported by a close similarity in terms of physicochemical and reactivity properties relevant for genotoxicity end points and in terms of mechanism of actions. "

As for the sub-chronic toxicity and the pre-natal developmental toxicity studies you have provided the following:

"The read-across analysis was performed for the toxicity super endpoint, including five endpoints, i.e. acute oral toxicity, acute dermal toxicity, acute inhalation toxicity, subchronic inhalation toxicity (90 days, rat) and prenatal developmental toxicity study, that were treated with the same reasoning in terms of mechanism action and for which the read-across follow a similar justification.
In the current study, methylal and dioxolane were selected by the commissioner as source chemicals or analogs, to predict the same endpoints for the target chemicals, i.e. ethylal [...], which were considered to be similar to source chemicals on the basis of structural similarity" and
" [...] methylal and dioxolane, was used to estimate the same toxicity endpoints for the target chemicals, i.e. ethylal, [...], which were considered to be "similar" enough according to their structural, mechanistic and physicochemical/reactivity property profiles to justify the read-across approach."

B. Information submitted by the Registrant to support the grouping approach and read-across hypothesis

In the dossier, Submission number: [redacted] you have provided the following information:

You have provided the read-across justification as attachments in the IUCLID file. You submitted separate read-across justification documents for the "*genotoxicity super endpoint*" (i.e. justifying predictions for the *in vitro* cytogenicity study in mammalian cells and the *in vivo* somatic cell genotoxicity) and for the "*toxicity super endpoint*" (i.e. justifying the predictions for the sub-chronic toxicity study (90-day) and the pre-natal developmental toxicity study). The documents contain the identification and structures of the analogue substances, the hypothesis, the justification, data matrices and supporting information (such as QSAR prediction and comparison of selected physico-chemical properties) for the "*genotoxicity super endpoint*" and for the "*toxicity super endpoint*", respectively.

The provided data matrices contain a summary of the available experimental studies on the source substances, QSAR predictions and the applied read-across for the target substance. Experimental test results on the source substances for genotoxicity, acute dose toxicity, repeated dose toxicity (90 days via inhalation) and pre-natal developmental toxicity are included in the data matrix.

For the genotoxicity endpoint supporting QSAR predictions on protein binding, DNA binding, micronucleus test and mutagenicity/carcinogenicity prediction are presented. For the sub-chronic toxicity and the pre-natal developmental toxicity endpoints supporting QSAR predictions on toxic hazard classification by Cramer; protein binding, oestrogen receptor binding are included in the above mentioned justification documents.

In the technical dossier and Chemical Safety report (CSR) you have provided oral, inhalation and dermal acute toxicity, skin and eye irritation, skin sensitisation, Ames test, *in vitro* gene mutation in mammalian cells test and a sub-acute (28 days) inhalation repeated dose toxicity study results from studies conducted with the registered substance.

C. ECHA analysis of the grouping approach and read-across hypothesis in light of the requirements of Annex XI, 1.5 as per dossier, Submission number: [redacted]

ECHA understands that your grouping approach as per dossier, Submission number: [redacted] is based on the similarity in the chemical structures of the selected substances, i.e. all substances contain an acetal moiety as a functional group and that the substances *"are characterized by the solely acetal functional group, thus they exhibit a very close structural similarity"* and *"which were considered to be "similar" enough according to their structural, mechanistic and physicochemical/reactivity property profiles to justify the read-across approach."*

Structural similarity and dissimilarity

You have identified the structural (dis)similarities between the target and source(s) as all substances contain an acetyl moiety as a functional group, namely two single bonded oxygen atoms attached to the same carbon atom. Differences occur in the length of the alkyl chains bound to the oxygen atoms by a single covalent bond. It is also emphasised in your documentation that the substances *"are characterized by the solely acetal functional group, thus they exhibit a very close structural similarity"*.

ECHA observes that the structural similarity of methylal (as a source substance) and ethylal (target substance) is properly described. They possess differences in the length of the linear alkyl chains having methyl and ethyl chains bound to the oxygen atoms, respectively. However, ECHA notes that structural similarity alone is not sufficient for predicting toxicological properties related to human health. This will be assessed in the subsequent sections.
In contrast to methylal, dioxolane has a cyclic chemical structure. You have explained that based on positive alerts for DNA/protein binding, dioxolane *"might exhibit a different genotoxic mechanism of action with respect to the targets ethylal and butylal"*. In light of the positive alert for the micronucleus test, the differences in the structure of the investigated acetals (cyclic vs linear) gain more relevance. However, you have not explained how the different structure of dioxolane might impact the other endpoints.

ECHA concludes that although you have addressed the structural differences between dioxolane and the target substance you have not explained why those differences would not indicate differences in the mode of action and in the toxicity profile of the target and source substances.

Given the structural differences between dioxolane and ethylal, ECHA considers that there is not an adequate basis for predicting the properties of ethylal from the data of dioxolane. On this basis alone the application of the read-across approach using the substance dioxoloane cannot be accepted.

Physico-chemical properties

You claim that similar physico-chemical properties of the target and source substances support the structural similarity. Selected physico-chemical and other properties relevant for genotoxicity, sub-chronic toxicity and pre-natal developmental toxicity were compared (molecular weight, refractivity, hydrophobicity, density, LogP, boiling point, H donors and H acceptors properties, molar volume and polar surface area (PSA), surface tension, polarizability and molecular refractivity, difference in HOMO and LUMO energies, reactivity or electrophilicity of the chemicals and vapour pressure) and you concluded that despite some small differences, the target and source chemicals are very similar to each other in terms of the investigated properties.

ECHA notes that the fact that physico-chemical and other parameters are similar may support the structural similarity, but cannot be used alone to justify a prediction on properties related to human health.

Toxicokinetic behaviour

ECHA observes that in the technical dossier you have provided an assessment of absorption, distribution and (bio)accumulation of the registered substance, but no data/assessment has been provided about metabolism relevant for the endpoints subject to the present read-across analysis. ECHA observes that from secondary sources (EFSA, WHO) it is known that in general, linear aliphatic acetals can be hydrolysed to their corresponding aldehydes and alcohols. The hydrolysis may be acid catalysed or enzymatic.

ECHA notes that no toxicokinetic data relevant for the endpoints subject to the present read-across analysis, has been provided on the source substances. Consequently, it is not possible to conclude whether there are differences in the toxicokinetic behaviour, in particular in metabolic fate / (bio)transformation of the substances and how any differences may influence the toxicity profile of the target and source substances.

ECHA considers that, based on the lack of toxicokinetic data, there is not an adequate basis for predicting the properties of ethylal from the data of the source substances.

QSAR predictions

You have provided QSAR predictions to support the proposed mechanism of action relevant for genotoxicity, repeated dose and the developmental toxicity and to predict toxicological properties (e.g. genotoxicity and structural dysmorphogenesis) of ethylal.

ECHA notes that the QSAR predictions for the gene mutation in mammalian cells, the *in vitro* chromosomal aberration test and for the *in vivo* micronucleus test could not be taken into account as supporting evidence since these predictions were outside the applicability domain of the applied model or similar compounds were not represented in the training set. In addition you assigned the reliability of these predictions as *"very little reliable"*.

You have also used the OECD QSAR Toolbox to profile the source and the target chemicals. These profilers gave negative alerts for two targets (ethylal and butylal) and two source substances (methylal and dioxolane), namely non-binding potential has been detected for them. However, dioxolane was found to have the possibility to chemically interact with DNA/proteins via covalent binding such as DNA intercalation or groove binding and gave a structural alert for the micronucleous test. You explain that *"a structural alert for micronucleous was identified suggesting that it might exhibit a different genotoxic mechanism of action with respect to the targets ethylal and butylal"*. This contradicts with your hypothesis that states that the substances' *"structural similarity is also supported by a close similarity [...] in terms of mechanism of actions"*.

As for the supporting QSAR predictions provided for the repeated dose toxicity (RDT) endpoint, ECHA notes that the applied QSAR Toolbox has only one profiler directly related to RDT, the RDT HESS. An RDT HESS alert hasn't been triggered, owing to the fact that the input substance was outside the applicability domain for that module. For the pre-natal developmental toxicity only the estrogen receptor binding and DART scheme profiler are related to the reproductive/developmental effects. ECHA notes that, due to the shortcomings explained above, the presented QSAR data cannot be used to justify the prediction of toxicological properties related to human health.

It should further be noted that the additional QSAR predictions on developmental toxicity (structural dysmorphogenesis in different species by Leadscope) have been excluded from ECHA's assessment due to their low reliability, as you indicated in the technical dossier.

Given the lack of relevant QSAR predictions for genotoxicity, repeated dose and developmental toxicity ECHA concludes that the presented QSAR data is not adequate for supporting the proposed similarity in the mechanism of action and to justify the predictions of toxicological properties related to human health.

Additional considerations concerning genotoxicity

In the data matrix, for the *in vitro* chromosomal aberration test you have provided negative results from an OECD 473 test conducted with methylal. You have stated that QSAR predictions for this endpoint are not applicable.
For the *in vivo* micronucleus test you have provided negative results from an OECD 474 test conducted with methylal. You have stated that QSAR predictions for this endpoint are *"little reliable"*.

ECHA understands that you propose to use methylal as source substance for the *in vitro* chromosomal aberration test and for the *in vivo* micronucleus test and the basis of the prediction is the similarity in the structure and in the mechanism of action relevant for genotoxicity.

ECHA observes that methylal *"induced gene mutations in a bacterial reversion assay (Ames test) without metabolic activation but not in mammalian (CHO) cells at the HPRT locus in the presence and absence of metabolic activation"*, as cited by EFSA (ref.: EFSA Journal 2011; 9(10):2312) but not mentioned in the ethylal dossier. Given that the Ames test results for ethylal were all negative this could indicate a difference in the mechanism of action relevant for the genotoxicity, between methylal and ethylal. Furthermore, other available genotoxicity test results on ethylal and methylal do not allow further comparison and do not confirm the similarity in the mode of action (i.e. different genotoxic properties of ethylal and methylal have been investigated by different test methods and results from similar or equivalent tests are not available which would allow for such a comparison).

Based on the findings listed above, and ECHA's general considerations of the read-across analysis, it cannot be confirmed that the target and source substance would have a similar or regular pattern with regard to the mechanism of action relevant for genotoxicity.

For the reasons set out above, ECHA therefore considers that there is not an adequate basis for predicting the properties of ethylal from the data of the source substance methylal.

Additional considerations concerning sub-chronic toxicity (90-day)

In the data matrix you have provided the NOAEL values of 6300 mg/m^3 and 903 mg/m^3 for methylal and dioxolane, respectively, based on inhalation sub-chronic toxicity (90-day) studies.

You have proposed that the source substances methylal and dioxolane have similar toxicity with regard to sub-chronic toxicity and therefore the properties of ethylal can be predicted from data obtained on the source substances.
In the technical dossier of the registered substance, you have submitted a predicted NOAEC value of 3127.89 mg/m^3 for ethylal, which is based on a weighted mean mathematical formalism using available NOAEC values of methylal and dioxolane. You have stated that instead of using the lower NOAEC value 903 mg/m^3 from dioxolane, which is the worst case scenario, you have used a weighted mean mathematical value, which is *"a more consistent prediction"*. ECHA notes that you have not disclosed the formalism and not justified its applicability. In addition, you have not explained why the *"weighted mode formalism"* is *"a more consistent prediction"* than a worst case approach.

Comparison of the sub-chronic inhalation toxicity of methylal and dioxolane reveals that the NOAEC values of methylal and dioxolane differ by about a factor of 7. This value could indicate a difference in the toxic potential of the substances. You have explained that the difference of the NOAEC values is arising from the fact the available tests with methylal and dioxolane *"have been performed by different labs with different sensitivity to define an adverse effect which is the basis of the NOAEC"*. On the other hand *"data of the source methylal was weighted less than the one of dioxolane, because of its much higher vapor pressure than the targets"*.

Based on these findings it is not possible to verify that the toxicity profile of the source substances is similar to that of the target substance.

For the registered substance, sub-acute (28 days) inhalation toxicity results are available ([redacted], test method: EPA TG 412). However, this study did not strictly follow the relevant OECD test guideline as you applied 12 days exposure over a period of 16 days and you followed an internal SOP, which is not further described in your dossier.

ECHA also notes that the additional QSAR predictions on repeated dose toxicity have been excluded from ECHA's assessment, as explained above.

ECHA further observes, that you have not submitted robust study summaries of the experimental data on the source substances in your dossier on ethylal.

In addition, you have not explained how the different structure of ethylal (linear) and dioxolane (cyclic) may impact the toxicity profile of the substances.

You have proposed that the source substances methylal and dioxolane have similar toxicity with regard to sub-chronic toxicity and therefore the properties of ethylal can be predicted from data obtained from the source substances. Given the lack of robust study summaries of the experimental data on the source substances, the missing explanation on the applied mathematical formalism and the uncertainty in the similarity of the toxicity profile of the substances, ECHA considers that there is not an adequate basis for predicting the sub-chronic toxicity properties of ethylal from the source substances methylal and dioxolane.

Additional considerations concerning pre-natal developmental toxicity

In the data matrix you have provided NOAEL values based on pre-natal developmental toxicity studies conducted with methylal (NOAELdev 31814 and NOAEL maternal 6174 mg/m^3) via inhalation and dioxolane (NOAELmaternal and dev 250 mg/kg bw/day; NOAEL dev 140 mg/kg bw/day, NOAELmaternal not defined in a non GLP study) via oral route.

ECHA observes that you have chosen methylal as an analogue substance based on the route of exposure: *"since the inhalation route is relevant for ethylal [...], the methylal data were read-across to ethylal"*. ECHA notes that the route of exposure alone is not acceptable as an adequate justification for the read across or for the choice of the source substance.

ECHA further notes that the additional QSAR predictions on developmental toxicity have been excluded from ECHA's assessment due to their low reliability and/or existing waivers you provided in the technical dossier as explained above. Additionally, you have not submitted robust study summaries of the experimental data on the source substance methylal.

You have proposed that the source substance methylal has similar toxicity with regard to pre-natal developmental toxicity and therefore the properties of ethylal can be predicted from data obtained from methylal.

Given the uncertainty in the similarity of the toxicity profile of target and source substance as explained under the sub-chronic toxicity endpoint, ECHA considers that there is not an adequate basis for predicting the properties of ethylal from the source substance, methylal.

D. Conclusion on the read-across approach as submitted in dossier, Submission number: [redacted]

ECHA considers that structural similarity alone is not sufficient for predicting toxicological properties related to human health. 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.

ECHA notes that in light 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 genotoxicity, repeated dose toxicity, or pre-natal developmental toxicity. Besides the reference to the structural similarity, there is no valid mechanistic explanation provided why predictions can be made using the results from the source substances. In contrast, some evidence contradicts that such predictions are possible.

ECHA considers that the read-across in its current form cannot be accepted due to the deficiencies explained above i.e. missing link of the structural similarities and (dis)similarities with the possibility to predict, lacking information on the adequacy and reliability of the source studies in the registration dossier, lacking information on the (bio)transformation/metabolism of source and target substances, uncertainty in the similarity or a regular pattern in the mechanism of action, in the toxicity profile of the source substances and the target substance.
Therefore, there is not an adequate basis for predicting the properties of ethylal from the analogue substances.

In your comments to the draft decision, under point 1, 3 and 5, you have indicated that you provided an updated IUCLID dossier with the following elements:

- removal of dioxolane (Pavan, 2016) from the source substances,
- further supporting information on toxicokinetic considerations, and
- the submission of Robust Study Summaries (RSS) on methylal used as source substance for the genotoxicity, the sub-chronic toxicity (90-day) and the pre-natal developmental toxicity endpoints.

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. All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation.

Irrespective of whether the newly provided information may be sufficient to meet the information requirement addressed in the decision, ECHA can already point out the following:

Based on the provided information ECHA understands that in your updated read-cross approach you propose to use only methylal as a source substance for all human health endpoints where read-across is proposed and subject to the present decision.

Removal of Dioxolane from the source substances

ECHA notes that in your updated read-across approach you have removed dioxolane from the source substances. ECHA observes that the removal of dioxolane from the source substances does not change ECHA's conclusions concerning the structural similarities, the physico-chemical properties and the QSAR prediction regarding ethylal and methylal as explained above in the "Structural similarity and dissimilarity" and "Physico-chemical properties" and "QSAR predictions" sections of this decision.

In particular, ECHA notes that the structural similarity and difference of methylal (as a source substance) and ethylal (target substance) is properly described. However, structural similarity between source and target substances alone is not sufficient for predicting toxicological properties related to human health.

You have concluded that despite some small differences, the target and source chemicals are very similar to each other in their physico-chemical properties. ECHA notes that the fact that physico-chemical and other parameters of source and target substances are similar may support the structural similarity, but cannot be used alone to justify a prediction on properties related to human health.

Toxicokinetics

The majority of the newly submitted supporting information on toxicokinetics is related to the metabolism and toxicokinetic behaviour of the source substance, methylal (Dahl & Hadley, 1983; Tomilina et al., 1984; [redacted]; Virtue, 1951[redacted]). ECHA observes that in the above mentioned studies different methods and (e.g. *in vitro* methods such as liver and nasal microsomes; *in vivo* methods such as repeated administration of methylal to rat via inhalation; *ex vivo* method such as using excised stomach of rats as a test system) and different route of administrations (e.g. intravenous, inhalation) were applied. ECHA observes that the results and conclusions from these studies do not provide clear evidence regarding the rate and extent of the metabolism of methylal. ECHA further notes that solely a brief summary of the above mentioned studies have been provided in the updated dossier and therefore, the adequacy and reliability of the data cannot be evaluated.

You claim that the *"UNEP Publications, 2004"* publication provides more information on the *"metabolism of degradation products of ethylal"*. ECHA observes that the mentioned study (SIDS Initial Assessment Report, 2004) is an assessment report on the substance ethanol. ECHA notes that this document does not contain any information on the toxickokinetic properties of ethylal.
You postulate in your statement document related to toxicokinetic similarity ([redacted]) that ethylal will hydrolyse into ethanol and formaldehyde. ECHA observes that none of the submitted supporting information provides evidence on the existence, the nature and extend of the hydrolysis of ethylal, the formation of ethanol as a postulated degradation products of ethylal.

ECHA further observes that the presented article on the *"general metabolism of acetals (EFSA, 2011)"* postulates that acetals may be hydrolysed to their corresponding aldehydes and alcohols via acid catalysed or enzymatic hydrolysis. However, it is pointed out in the document that *"There is very little information available on hydrolysis of the candidate acetals in the present flavouring group (FGE.03Rev2). From available data on supporting substances as well as on acetals with differing chemical structures it is clear that the rates of both acid hydrolysis and enzymatic hydrolysis will vary with different chemical structure of the acetals, and that hydrolysis sometimes may be slow and incomplete. Data submitted show that the rate of hydrolysis may vary considerably, even within groups of closely related substances with simple structures. The rate of hydrolysis may also depend on the solubility of the substance in aqueous media."* Most importantly it is concluded that *"There is currently not enough information to draw general conclusions on hydrolysis rates of acetals."* and in chapter *"In vivo biotransformation of acetals"* were emphasised that *"These findings indicate that rates of acetal acid hydrolysis may vary considerably, depending on molecular structure, even within this group of closely related substances"*. In addition, ECHA notes that this document does not provide more insight or clear evidence on the metabolism and toxicokinetic behaviour of ethylal (the target substance).

Moreover, in your statement document ([redacted]) you draw the same conclusion as the above mentioned study *(EFSA, 2011)*: *"The data from studies on hydrolysis in vitro as well as the in vivo studies show that the time for hydrolysis may vary greatly even within groups of very closely related substances. Hydrolysis data on compounds with structural similarity to the candidate substances show that the candidate acetals may be predicted to be hydrolysed. However, it cannot be excluded that some amounts of the parent acetals may reach the systemic circulation."*

In addition, you note in the same place that: *"Note that the in silico analysis of the ADME properties and toxicokinetic (TK) behavior of the 2 acetals (methylal, ethylal) is not provided since the 2 acetals resulted to be out of the applicability domain of the employed predictors."*

In summary, the provided information is not sufficient to draw a conclusion on the toxicokinetic/(bio)transformation profile of the target and source substances and on the differences in the toxicokinetic behaviour, in particular in metabolic fate / (bio)transformation of source and target substances. Consequently, it is not possible to conclude whether and how the possible differences may influence the toxicity profile of the target and source substances. ECHA considers that based on the aforementioned there is not an adequate basis for predicting the properties of ethylal from the data of the source substance methylal.

Additional consideration concerning the genotoxicity, the sub-chronic toxicity (90 day), the pre-natal developmental toxicity are outlined in the relevant sections (Section 1, 2, 3 and 5, below).

Reliability of the source studies

You state in your comments to the draft decision that *"The Robust Study Summaries (RSS) of methylal used as source substance have been provided."* By the reason that the proposed adaptation of the information requirement based on the updated read-across approach is not accepted, ECHA has not assessed the provided Robust Study Summaries (RSS) on methylal (source substance) for compliance with the REACH requirements.

Conclusion on the read-across approach
Pursuant to Article 41(1) of the REACH Regulation, ECHA concludes that the adaptation of the standard information requirements for the endpoints *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2); *in vivo* somatic cell genotoxicity (Annex IX, Section 8.4. column 2); sub-chronic toxicity study (90-day; Annex IX, Section 8.6.2.) and pre-natal developmental toxicity study (Annex IX, Section 8.7.2) in the technical dossier as submitted in Submission number: [redacted] and Registrants comments on the draft decision based on the proposed read-across approach does not comply with the general rules of adaptation as set out in Annex XI, 1.5. Therefore, ECHA rejects all adaptations in the technical dossier as submitted in Submission number: [redacted] that are based on Annex XI, 1.5.

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

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) 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.

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

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing results of an *in vitro* cytogenicity study in mammalian cells (OECD TG 473) with the analogue substance methylal (CAS no 109-87-5). However, as explained in the section '*Grouping of substances and read-across approach*' of this decision, your adaptation of the information requirement cannot be accepted.

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 EU B.10./OECD TG 473) and the *in vitro* micronucleus test (OECD TG 487) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.2. of the REACH Regulation.

In your comments to the draft decision, under point 1, 3 and 5, you have indicated that you provided an updated IUCLID dossier where the read-across approach has been updated (Pavan, 2016) with the following elements: removal of dioxolane from the source substances, further supporting information on toxicokinetic considerations and the submission of Robust Study Summaries (RSS) on methylal used as source substance.

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. All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation.

Irrespective of whether the newly provided information may be sufficient to meet the information requirement addressed in this decision, ECHA can already point out the following:

You explain in your comments that *"This point has been filled in the initial dossier by providing an in vitro cytogenicity study in mammalian cells (OECD TG 473) with the analogue substance methylal (CAS no 109-87-5)."* however *"no test performed according to OECD TG 473 is available for methylal. This test has been performed according to OECD TG 476. [...] The strategy of the updated read-across is therefore to refer to endpoint "OECD Guideline 474 - Mammalian Erythrocyte Micronucleus Test" from source methylal [...] Existing OECD TG 474 test with methylal is considered to be an adequate data."*

ECHA observes that your dossier Submission number: [redacted] and read across approach contained results of the OECD TG 473 with methylal which were used as a source study. Based on the provided new information ECHA understands that in your updated read-cross approach you intend to use the OECD TG 474 study with methylal as a source study.

You claim in your comments to the draft decision that *"It is important to note that no alert has been found among the 6 mechanistic profilers relevant for genotoxicity with source methylal and target ethylal, supporting the similarity of toxicokinetic behaviours of both compounds."*

ECHA observes that you have updated your genotoxicity profiling in your updated dossier by replacing

- the DNA binding by OECD (mechanistic profiler)
- DNA binding by OASIS (mechanistic profiler)
- Micronucleus alerts by Benigni/Bossa (endpoint specific profiler)
- and the Mutagenicity/Carcinogenicity alerts by Benigni/Bossa (endpoint specific profiler)

with

- DNA alerts for AMES, MN and CA by OASIS v.1.3 (endpoint specific profiler)
- in vitro mutagenicity (Ames test) alerts by ISS (endpoint specific profiler)
- in vivo mutagenicity (Micronucleus) alerts by ISS (endpoint specific profiler).
- Protein binding alerts for Chromosomal aberration by OASIS v1.1 (endpoint specific profiler).

ECHA notes that you have not indicated the reliability of the applied models and whether the substances are in the applicability domian of the models. Moreover, you have not explained how the absence of the alerts in the genotoxcity profilers would support the similarity of toxicokinetic behaviours of target and source substances.

ECHA observes that in your comments to the draft decision you intend to explain the difference in the mechanism for genotoxicity as highlighted in the initial read-across analysis by ECHA. You refer to additional studies with the source substance methylal (Ames tests, an OECD TG 476 and an OECD TG 474 study) which show negative results. You propose that negative results in these studies support the absence of positive genotoxicity effects in methylal.

ECHA considers that with regard to the updated read-across approach and the submitted new information the same observations and considerations are valid as explained under the section *"Grouping of substances and read-across approach"* in Appendix 1 of the current decision.

ECHA notes that the provided studies might support the absence of positive effects in genotoxicity with methylal. ECHA has not assessed the provided Robust Study Summaries (RSS) on methylal (source substance) for compliance with the REACH requirements.

ECHA observes that you have not provided new genotoxicity information on the target substance ethylal. Moreover, you explain that the positive result observed with ethylal in an *in vitro* mammalian cell gene mutation originates from a study (Seifried, 2006) of which relevance *"is questioned (Klimisch code 3) and is not considered in the read-across approach"*. Irrespective of the reliability level of the above mentioned study, the initial consideration by ECHA, that the *"available genotoxicity test results on ethylal and methylal do not allow further comparison and do not confirm the similarity in the mode of action (i.e. different genotoxic properties of ethylal and methylal have been investigated by different test methods and results from similar or equivalent tests are not available which would allow for such a comparison)"* is still valid.

Consequently, he information gap is valid and it is necessary to provide the requested information.
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* cytogenicity study in mammalian cells (test method: EU B.10./OECD TG 473) or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487).

Notes for your consideration:

The *in vitro* genotoxicity study (OECD TG 473 or 487) should be performed before the *in vivo* genotoxicity study requested in the next section, as the result of the *in vitro* study can be taken into account when deciding on the *in vivo* test to be performed.

2. Transgenic rodent somatic and germ cell gene mutation assays (Annex IX, Section 8.4., column 2)

OR

In vivo mammalian alkaline comet assay (Annex IX, Section 8.4., column 2)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) 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.

"Mutagenicity" is an information requirement as laid down in Annex VIII, Section 8.4. of the REACH Regulation. Column 2 of Annex IX, Section 8.4. provides that "If there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII and there are no results available from an *in vivo* study already, an appropriate *in vivo* somatic cell genotoxicity study shall be proposed by the Registrant."

The technical dossier contains an *in vitro* mammalian cell gene mutation test performed according to OECD TG 476 (key study, Seifried 2006 and 2008) with the registered substance that shows positive results with metabolic activation. The positive results indicate that the substance is inducing gene mutations under the conditions of the test.

You have sought to adapt the *in vivo* somatic cell genotoxicity (Annex IX, Section 8.4., column 2) information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing an *in vivo* mammalian erythrocyte micronucleus test (OECD TG 474) in mouse, with the analogue substance methylal (CAS no 109-87-5). However, as explained in the section '*Grouping of substances and read-across approach*' of this decision, your adaptation of the information requirement cannot be accepted.

According to the ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, July 2015) Chapter R.7a, section R.7.7.6.3, the transgenic rodent somatic and germ cell gene mutation assays ("TGR assay", OECD TG 488) and the *in vivo* mammalian alkaline comet assay ("comet assay", OECD TG 489) are suitable to follow up a positive *in vitro* result on gene mutation.

Hence, ECHA considers that the TGR and the comet assay are suitable tests to follow up the concern on gene mutation for the substance subject to the decision.

Therefore, ECHA concludes that an appropriate *in vivo* genotoxicity study to follow up the concern on gene mutations is not provided for the registered substance. Consequently there is an information gap and it is necessary to provide information for this endpoint.

Considerations on the species and route to be used for testing

In case you decide to perform the TGR assay according to the test method EU B.58/OECD TG 488, the test shall be performed in transgenic mice or rats. ECHA has evaluated the most appropriate route of administration for the study. Since the registered substance is a liquid of very high vapour pressure (>10 kPa) and human exposure by the inhalation route is reported in the registration, ECHA considers that the inhalation route is the most appropriate route of administration.

In case you decide to perform the comet assay according to the test method OECD TG 489, the test shall be performed in rats. Having considered the anticipated routes of human exposure and adequate exposure of the target tissue(s) performance of the test by the inhalation route is appropriate. ECHA has evaluated the most appropriate route of administration for the study. Since the registered substance is a liquid of very high vapour pressure (>10 kPa) and human exposure by the inhalation route is reported in the registration dossier, ECHA considers that the inhalation route is the most appropriate route of administration.

In case you decide to perform a TGR assay according to the test method EU B.58/OECD TG 488, the test shall be performed by analysing tissues from liver as slowly proliferating tissue and primary site of xenobiotic metabolism, and from lungs as site of direct contact. In case you decide to perform a comet assay according to the test method (OECD TG 489), the test shall be performed by analysing tissues from liver as primary site of xenobiotic metabolism and lungs as sites of contact.

Furthermore, in your comments to the draft decision, you explain that *"This point is requested because of the positive result observed in vitro mammalian cell gene mutation study. [...] this positive result comes from a mouse lymphoma evaluation of hundreds of substances among which ethylal is listed with absence of details on purity and raw data (Seifried, 2006)."*

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. All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation.

Irrespective of whether the newly provided information may be sufficient to meet the information requirement addressed in this decision, ECHA can already point out the following:

ECHA observes that you have indicated the above mentioned study as key study (reliability 2) in the dossier as submitted in dossier, Submission number: [redacted] however you changed the reliability of the study from a reliability of 2 in the dossier Submission number: [redacted] to a reliability of 3 in your updated dossier.

ECHA further observes that as submitted in dossier, Submission number: [redacted] and in your updated dossier, both submissions contain raw data on the above mentioned *in vitro* mammalian cell gene mutation study with ethylal (Seifried, 2006). ECHA considers that you have not justified sufficiently why the above mentioned study *(Seifried, 2006)* is not appropriate anymore to be graded as a key study (reliability 2). In addition, ECHA considers that the provided information in the publication (Seifried, 2006) is sufficient to consider the result of the *in vitro* mammalian cell gene mutation in mouse lymphoma cell test as positive. Hence ECHA concludes that the study can be still regarded as reliability 2, key study.

Furthermore, ECHA notes that you express your intention to improve the genotoxicity data set: *"Regarding the relevance of the positive result (Klimisch code 3), it may be anticipated to generate a transgenic rodent somatic and germ cell gene mutation assays (OECD 488) or in vivo mammalian alkaline comet assay (OECD 489). The strategy is to perform a new Ames test and new in vitro mammalian cell gene mutation study according to state-of-the art guidelines."* In the same time ECHA observes, that you have not provided any new *in vitro* mammalian cell gene mutation study on ethylal with higher reliability than your original key study. Thus ECHA notes that currently no data is available on ethylal which would overrule the positive results observed in the *in vitro* mammalian cell gene mutation study (Seifried, 2006).
In summary, ECHA considers that the observed positive results (Seifried, 2006) are valid and indicate that the substance is inducing gene mutations under the conditions of the test and the concern on gene mutation has to be followed up by an appropriate *in vivo* genotoxicity test.

ECHA considers that with regard to the updated read-across approach and the submitted new information the same observations and considerations are valid as explained under the section *"Grouping of substances and read-across approach"* in Appendix 1 of the current decision.

Consequently, the information gap is valid and it is necessary to provide the requested information.

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:

Transgenic rodent somatic and germ cell gene mutation assays (test method: EU B.58/OECD TG 488) in transgenic mice or rats, inhalation route on the following tissues: liver, lungs.

OR

In vivo mammalian alkaline comet assay (test method: OECD TG 489) in rats, inhalation route, on the following tissues: liver, lung.

Notes for your consideration:

The chosen *in vivo* genotoxicity study (OECD 488 or 489) shall be performed after obtaining the results of the *in vitro* genotoxicity study (OECD 473 or 487) that is requested in the previous section and the results of the *in vitro* study should be taken into account when deciding on the *in vivo* genotoxicity study.

If the results of the *in vitro* study demonstrate a concern for chromosomal aberrations, please note that it is a requirement that 'appropriate *in vivo* mutagenicity studies shall be considered in case of a positive result in any of the genotoxicity studies in Annex VII or VIII' and you should consider to perform the *in vivo* mammalian alkaline comet assay (OECD 489). ECHA considers that the *in vivo* mammalian alkaline comet assay (OECD 489) is the most suitable *in vivo* test to follow up positive result *in vitro* testing showing chromosomal aberrations and equivocal information on gene mutagenicity. ECHA also notes that following the principle of replacing, reducing and refining animal testing (the 3Rs principle), the combination of *in vivo* genotoxicity studies, whenever possible and when scientifically justified, is strongly encouraged and that the TG 489 provides the option to combine the *in vivo* mammalian alkaline comet assay with other genotoxicity tests, e.g. which could address a concern for cytogenicity.

Furthermore, you are reminded that according to Annex IX, Section 8.4., column 2 of the REACH Regulation, if positive results from an *in vivo* somatic cell study are available, "*the potential for germ cell mutagenicity should be considered on the basis of all available data, including toxicokinetic evidence. If no clear conclusions about germ cell mutagenicity can be made, additional investigations shall be considered*".

In case you decide to perform the TGR assay, you shall collect male germ cells (see OECD TG 488, paragraph 33). Male germ cells shall be collected at the same time as the other tissues (liver and lung), and stored up to 5 years (at or below −70 ºC). This duration is sufficient to allow the Registrant or ECHA, in accordance to Annex X, Section 8.4., column 2, to decide on the need for assessment of mutation frequency in the collected germ cells.

In case you decide to perform the comet assay, you may consider examining gonadal cells, as it would optimise the use of animals. ECHA notes that a positive result in whole gonads is not necessarily reflective of germ cell damage since gonads contain a mixture of somatic and germ cells. However, such positive result would indicate that the substance and/or its metabolite(s) have reached the gonads and caused genotoxic effects. This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

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

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) 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.

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing sub-chronic inhalation toxicity studies with the analogue substances methylal (CAS no 109-87-5) and 1,3-dioxolane (CAS no 646-06-0). However, as explained in the section '*Grouping of substances and read-across approach*' of this decision, your adaptation of the information requirement cannot be accepted.

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. Since the registered substance is a liquid of very high vapour pressure (>17 kPa at 20 °C) and human exposure by the inhalation route is reported in the registration, ECHA considers that the inhalation route is the most appropriate route of administration. Hence, the test shall be performed by the inhalation route using the test method OECD TG 413.

According to the test method OECD TG 413 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

In your comments to the draft decision, you have indicated that you provided an updated IUCLID dossier where the read-across approach has been updated with the removal of dioxolane from the source chemicals, further supporting information on toxicokinetic considerations and the submission of Robust Study Summaries (RSS) on methylal used as source substance.

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. All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation.

Irrespective of whether the newly provided information may be sufficient to meet the information requirement addressed in this decision, ECHA can already point out the following:

With regard to the updated read-across approach and the submitted toxicokinetic information the same observations and considerations are valid as explained under the section *"Grouping of substances and read-across approach"* in Appendix 1 of the current decision.

With regard to the comparison of the available short term inhalation studies with methylal and ethylal ECHA oserves the following:

- The mentioned 22d repeated dose inhalation *"([redacted], 1996)"* was performed in 1969 and not in 1996 as indicated by you and was not in accordance with the GLP requirements. Furthermore, the aim of the study was to compare the repeated inhalation toxicity of methylal with Aeothene MM and Aerothene TT and applied only one dose group for methylal. The other tested substances were mixtures, containing only 3 % w/w of methylal. The additional components of the mixture were the substances Aerothene MM or Aerothene TT and tertiary butyl alcohol. Hence, ECHA concludes that this study does not provide a reliable basis for comparing the effects of pure substances (i.e. methylal with ethylal).
- After comparison of the result of the OECD TG 413 with methylal ([redacted]) and the EPA TG 412 study with ethylal ([redacted]) ECHA concludes that your claim *"these studies (2 with methylal and 1 with ethylal) are characterised by an absence of adverse effects by inhalation route, supporting the same toxicokinetic profile of methylal and ethylal"* is not supported by the presented data as explained below:

In the OECD 413 inhalation study with methylal in the highest dose group, in both sexes slightly increased liver weights and transient disequilibrium, uncoordinated gait, ataxic gait and decreased spontaneous activity due to anaesthetic effect were recorded.
Contrary, the sub-acute inhalation study with ethylal ([redacted]) did not show transient CNS effects. Moreover, in addition to the statistically significant increases in liver weights in males and females exposed to highest dose, the observed effects were different form the ones observed with methylal, such as small but statistically significant increase in adrenal gland weights in females exposed to highest dose which were considered test substance related. Furthermore, the mid and high dose group females showed slightly lower mean corpuscular haemoglobin which was statistically significant.

- Therefore ECHA concludes that the presented evidence contradicts the claimed similarity of toxicity profiles.

In addition, ECHA observes the following: in your comments you claim that *"It is important to note that no alert has been found among the mechanistic profilers relevant for repeated dose toxicity with source methylal and target ethylal, supporting the similarity of toxicokinetic behaviours of both compounds."*

ECHA notes that the above claim contradicts with your statement in chapter *"Repeated dose toxicity HESS profiler (v2.6)"* of the attached read-across justification document, which clearly explains that an RDT HESS - the profiler directly related to RDT- alert hasn't been triggered, owing to the fact that the input substances were outside the applicability domain for that module:
"Finally, the two target compounds Ethylal and Butylal and the source Methylal don't answer any of the categorization criteria of the Repeated Dose Toxicity HESS Profiler since they are out of the applicability domain for that module." Hence, the presented information could not be taken into account to support the similarity of toxicokinetic behaviour of target and source substances.

Consequently, the information gap is valid and it is necessary to provide the requested information.

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: Sub-chronic inhalation toxicity: 90-day study (test method: OECD TG 413) in rats.

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

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) 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.

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

You have sought to adapt this information requirement according to Annex VIII, Section 8.7.1., column 2. You provided the following justification for the adaptation:

i. *"According to column 2 « Specific rules for adaptation from column 1 » in Annex VIII of REACH, this study does not need to be conducted if a pre-natal developmental toxicity study (Annex IX, 8.7.2) or a two-generation reproductive toxicity study or QSAR (Annex IX, Section 8.7.3) is available and that results are not of concern.*

ii. *According to column 1 "Standard information required" in Annex IX of REACH, the test is needed if the 28-day or 90-day study indicates adverse effects on reproductive organs or tissues. No adverse effects have been recorded in testes, epididymides, male accessory sex glands, ovaries, vagina, uterus and Fallopian tubes in rats exposed to 3000 ppm of ethylal in the 2-week inhalation toxicity ([redacted]). "*

With regard to the first argument ECHA notes that your adaptation on the standard information requirements "sub-chronic toxicity study (90 day)" and "pre-natal developmental toxicity study" cannot be accepted as explained in the section 'Grouping of substances and read-across approach' of this decision. Moreover, 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

With regard to the second point, ECHA points out that this is not an adaptation provision for the screening for reproductive/developmental toxicity study but a provision that describes under which conditions an extended one-generation reproductive toxicity study is required. The consideration of this provision is applicable once results of the repeated dose toxicity (90-day) study with the registered substance are available.

Therefore, 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 methods OECD TG 421 or 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.

In your comments to the draft decision, you sought to adapt this information requirement according to Annex VIII, Section 8.7.1., column 2:*"as [it is] not considered as a legal requirement (based on the REACH Annex IX, 8.7.1 column 2 adaptation) but rather as a recommendation from ECHA guidance R7."*

ECHA notes the following:
"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. Currently no such evidence is presented in the dossier.
In addition ECHA notes that currently none of the Annex VIII, Section 8.7.1 column 2 adaptation requirements is fulfilled.

The Guidance on information requirements and chemical safety assessment, Chapter R.7 addresses the importance of conducting an OECD TGs 421 or 422 screening study:

"The screening studies provide initial information of the effects on male and female reproductive performance as well as on developmental toxicity during and shortly after birth, as well as certain additional parameters for endocrine disrupting mode of action including anogenital distance, nipple/areola retention, thyroid hormone levels as given in the revised TGs (2015)."

"However, since the fertility and reproductive performance and developmental toxicity manifested shortly after birth are not assessed in a prenatal developmental toxicity study, it is strongly recommended to also conduct an OECD TGs 421 or 422 screening study as already discussed earlier (a testing proposal is not needed for a screening study)."

"Where a screening test is omitted based on a prenatal developmental toxicity study and an extended one-generation reproduction toxicity study is not triggered at REACH Annex IX level, then information on fertility would be limited to evaluation of the reproductive organs after repeated dosing, if those studies are available. Where information from a reproductive toxicity study addressing a fertility endpoint is not available, it is strongly recommended that a screening study is considered to fulfil this endpoint."

In addition, an OECD TGs 421 or 422 screening study can provide valuable information on the selection of the highest dose level in the requested prenatal developmental toxicity study and sub-chronic toxicity study (90-day).

Consequently, the information gap is valid and it is necessary to provide the requested information.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision:

Reproductive/developmental toxicity screening test (test method: OECD TG 421) *or*
Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

Notes for your considerations

For the selection of the appropriate test, please consult ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, section R.7.5 and 7.6 (version 4.1, October 2015).

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

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) 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.

A "pre-natal developmental toxicity study" for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.
You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a pre-natal developmental toxicity study with the analogue substance methylal (CAS 109-87-5). However, as explained in the section '*Grouping of substances and read-across approach*' of this decision, your adaptation of the information requirement cannot be accepted.

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 4.0, July 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 comments to the draft decision, under point 1, 3 and 5, you have indicated that you provided an updated IUCLID dossier read-across approach has been updated (Pavan, 2016) with the following elements: removal of dioxolane from the source substances, further supporting information on toxicokinetic considerations and the submission of Robust Study Summaries (RSS) on methylal used as source substance.

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. All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation.

Irrespective of whether the newly provided information may be sufficient to meet the information requirement addressed in this decision, ECHA can already point out the following:

With regard to the updated read-across approach and the submitted toxicokinetic information the same observations and considerations are valid as explained under the section *"Grouping of substances and read-across approach"* in Appendix 1 of the current decision.

Hence, ECHA considers that the proposed adaptation of the information requirement based on the updated read-across approach does not comply with the general rules of adaptation as set out in Annex XI, 1.5 and cannot be accepted.

Consequently, the information gap is still valid and it is necessary to provide the requested information.

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 (rats or rabbits) by the oral route.

6. Robust study summary for key study, Ewell WS, Gorsuch JW, Kringle RO (1986), Simultaneous Evaluation of the Acute Effects of Chemicals on Seven Aquatic Species (Environmental Toxicology and Chemistry, Vol. 5, pp 831-840, 1986) (Annex VII, Section 9.1.1. in conjunction with Annex I, Section 3.1.5);

Pursuant to Articles 10(a)(vi) and 12(1)(e) 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.

Pursuant to Articles 10(a)(vii) of the REACH Regulation, the information set out in Annex VII to XI must be provided in the form of a robust study summary, if required under Annex I. Article 3(28) defines a robust study summary as a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study minimising the need to consult the full study report. Guidance on the preparation of the robust study summaries is provided in the ECHA Practical Guide 3: 'How to report robust study summaries' (Version 2.0, November 2012).

"Short-term toxicity testing on aquatic invertebrates", is a standard information requirement as laid down in Annex VII, Section 9.1.1. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement. Furthermore, pursuant to Article 10(a)(vii) and Annex I, Section 3.1.5. if there are several studies addressing the same effect, then, the study or studies giving rise to the highest concern shall be used to draw the conclusion and a robust study summary shall be prepared for that study or studies and included as part of the technical dossier. Robust summaries will be required of all key data used in the hazard assessment.

In the technical dossier you have provided a study record *"Simultaneous Evaluation of the Acute Effects of Chemicals on Seven Aquatic Species (Environmental Toxicology and Chemistry, Vol. 5, pp 831-840, 1986)"* with the registered substance, which you describe as *"not GLP, not following OECD guidelines but high quality international protocol"* to meet the standard information of Annex VII, Section 9.1.1.

Further, in the Overall remarks section of this robust study summary you note: "[redacted], *formally an operating Division of* [redacted] *is well aware of the historical procedures utilized in the* [redacted] *to conduct simultaneous aquatic toxicity tests utilizing seven aquatic species. A summary of those procedures was published in the peer reviewed journal article referenced here. In addition* [redacted] *has provided a copy of a protocol (*[redacted]*) that was utilized within the laboratory during that period of time. While the provided protocol is not for the specific test conducted with diethoxymethane (CAS # 462-95-3), the protocol was the standard basis of testing conducted during that time period. The protocol allowed for some modifications such as the type of exposure (static or flow through) and nominal or measured test substance solutions. While records of the actual test with diethoxymethane (CAS # 462-95-3) are limited to a summary of the results,* [redacted] *is certain that the test was conducted under the procedures outlined in the protocol and published journal article. In addition, the summary of results indicate that due to the volatility of the test substance the test was conducted using a flow-through design at two nominal concentrations (2500 and 250 mg/L), and the results are based upon the mean values of the analytically verified exposure concentrations measured at test initiation, 24, 48, and 96 hours. Therefore,* [redacted] *believes that this test and the procedures utilized during that time period are equivalent to current methodologies, reliable, and provide data that is applicable for evaluation of the hazard of this test substance."*

ECHA notes the following:

a. There is a reference to a protocol attached. However, ECHA could not find this protocol in the dossier. A mere reference to a study published in a scientific journal is not sufficient.

b. The robust study summary lacks details in the following sections (most important omissions specified):
   1. Test material: purity (and potential impurities) not reported
   2. Sampling and analysis: no details reported
   3. Test solutions: no details reported
   4. Test organisms: seven organisms are reported, but ECHA assumes that you want to refer to *Daphnia magna* for this robust study summary
   5. Test conditions: pH, dissolved oxygen; reference substance reported as '*diluent water*'
   6. Results and discussion: details on results (e.g. in tabular format), positive control, statistics
   7. Applicants summary and conclusion: it is not clear how you concluded that the validity criteria of the study have been fulfilled

Overall, the reporting is not adequate. ECHA considers this lack of information undermines the reliability of the test results of the study. Especially the lack of detailed information on the analytical monitoring (e.g. number of sampling point during the test) is important since the substance has a relatively high vapour pressure (17 kPa is reported in your technical dossier) and volatilisation of the test substance during testing cannot be excluded.

Finally, ECHA notes that apparently only 2 concentrations with a very wide spacing have been tested (250 and 2500 mg/L). If this is the case, a reliable EC50 cannot be derived from this study.

Therefore, ECHA notes that, contrary to Article 3(28) of the REACH Regulation the documentation of this study is insufficient and does not allow an independent assessment of the adequacy of this study, its results and its use for hazard assessment. In particular, the above mentioned elements are missing.

Since the outcome of this study is used in your chemical safety assessment and as a result also to adapt the information requirements for long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5) and long-term toxicity testing on fish (Annex IX, Section 9.1.6.1) pursuant to Article 41(1) and (3) of the REACH Regulation you are requested to provide a complete robust study summary with the above missing elements for this study.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information: Robust study summary for the key study Ewell WS, Gorsuch JW, Kringle RO (1986), Simultaneous Evaluation of the Acute Effects of Chemicals on Seven Aquatic Species (Environmental Toxicology and Chemistry, Vol. 5, pp 831-840, 1986).

7. Robust study summary for key study, Eastman (1994), Diethoxymethane MSDS (Annex VIII, Section 9.1.3. in conjunction with Annex I, Section 3.1.5);

Pursuant to Articles 10(a)(vi) and 12(1)(e) 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.

Pursuant to Articles 10(a)(vii) of the REACH Regulation, the information set out in Annex VII to XI must be provided in the form of robust study summary, if required under Annex I. Article 3(28) defines a robust study summary as a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study minimising the need to consult the full study report. Guidance on the preparation of the robust study summaries is provided in the ECHA Practical Guide 3: 'How to report robust study summaries' (Version 2.0, November 2012).

"Short-term toxicity testing on fish", is a standard information requirement as laid down in Annex VIII, Section 9.1.3. 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. Furthermore, pursuant to Article 10 (a)(vii) and Annex I, Section 3.1.5. if there are several studies addressing the same effect, then, the study or studies giving rise to the highest concern shall be used to draw the conclusion and a robust study summary shall be prepared for that study or studies and included as part of the technical dossier. Robust summaries will be required of all key data used in the hazard assessment.

In the technical dossier you have provided a study record "*Eastman (1994), Diethoxymethane MSDS*" with the registered substance to meet the standard information requirement of Annex VIII, Section 9.1.3.

ECHA notes the following:

a. There is a reference to IUCLID section 6.1.3 for the protocol used. As explained above under 6 ECHA could not find this protocol in the dossier. A mere reference to a study published in a scientific journal is not sufficient.

b. The robust study summary lacks details in the following sections (most important omissions specified):
   1. Test material: purity (and potential impurities) not reported
   2. Sampling and analysis: no details reported
   3. Test solutions: no details reported
   4. Test conditions: pH, dissolved oxygen; reference substance reported as *'diluent water'*
   5. Results and discussion: details on results (e.g. in tabular format), positive control, statistics
   6. Applicants summary and conclusion: it is not clear how you concluded that the validity criteria of the study have been fulfilled

Overall, the reporting is not adequate. ECHA considers this lack of information undermines the reliability of the test results of the study. Especially the lack of detailed information on the analytical monitoring (e.g. number of sampling point during the test) is important since the substance has a relatively high vapour pressure (17 kPa is reported in your technical dossier) and volatilisation of the test substance during testing cannot be excluded.

Finally, ECHA notes that apparently only 2 concentrations with a very wide spacing have been tested (250 and 2500 mg/L). If this is the case, a reliable LC50 cannot be derived from this study.

Therefore, ECHA notes that, contrary to Article 3(28) of the REACH Regulation the documentation of this study is insufficient and does not allow an independent assessment of the adequacy of this study, its results and its use for hazard assessment. In particular, the above mentioned elements are missing.

Since the outcome of this study is used in your chemical safety assessment and as a result also to adapt the information requirements for long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5) and long-term toxicity testing on fish (Annex IX, Section 9.1.6.1) pursuant to Article 41(1) and (3) of the REACH Regulation you are requested to provide a complete robust study summary with the above missing elements for this study.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information: Robust study summary for the key study Eastman (1994), Diethoxymethane MSDS.

8. Simulation testing on ultimate degradation in surface water (Annex IX, Section 9.2.1.2.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) 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.

"Simulation testing on ultimate degradation in surface water" is a standard information requirement as laid down in Annex IX, 9.2.1.2 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 QSAR prediction estimating a half-life of 141 hours and have concluded, in the PBT assessment, that the substance is not considered to fulfil the P criterion. You also provided a 1996 5-day study where no biodegradation was observed.

ECHA notes that, based on the provided QMRF and QPRF documents, it is unclear whether the prediction is for biotic or abiotic degradation. Furthermore, the predicted endpoint is not well defined. Indeed, in the QPRF section 3.1, the addressed endpoint is called "*Ready Biodegradability (Aerobic Mineralisation in Surface Water – Simulation Biodegradation Test) OECD 309*", which introduces unclarity on whether the prediction addresses ready biodegradation or if it is expected to cover a simulation test.

There is also uncertainty concerning the training set used. Indeed, in the QMRF section 9.1 reports that "*The data are gathered from handbook (Physical-Chemical Properties and Environmental Fate Handbook) which includes data from different sources. Therefore the experimental protocol cannot be provided*". As a consequence, it is not known which were the test guidelines for the training set results. In addition, it is stated in the QPRF section 3.3.c) that "*the range of the experimental values is categorized rather than continuous*", namely the exact measured half-life of the training set compounds is not known. Moreover, information on the identification of any degradation products is not present in the dossier, whilst the reasons for the high deviations of the QSAR prediction with the screening study have not been addressed.

The provided QSAR prediction does not meet the conditions listed in REACH Annex IX, 1.3, as its results are not derived from a (Q)SAR model whose scientific validity has been established (first OECD principle for QSAR validation not fulfilled) and they are not adequate for the purpose of classification and labelling and/or risk assessment.

In the present dossier, ECHA notes that the information on this endpoint is not available. The technical dossier does not either contain an acceptable adaptation for this standard information requirement in accordance with Column 2 of Section 9.2.1.2 of Annex IX (as the substance is not readily biodegradable and it is not highly insoluble in water) or Annex XI to the REACH Regulation.

Taking into account the above, ECHA considers that the information provided on degradation of the substance in the technical registration dossier or in the Chemical Safety Assessment (CSA) is not sufficient to demonstrate absence of the need for further information on degradation and the relevant transformation and/or degradation products in surface water.

In your comments to the draft decision, you have indicated that you provided a modified QPRF and a training set in an updated dossier.

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. All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation.

Irrespective of whether the newly provided information may be sufficient to meet the information requirement addressed in this decision, ECHA can already point out the following: the validity of the model used for simulation testing and the identification of degradation products cannot be established because of the scarce documentation about the data quality of values used in the training set. There is no indication of the test guidelines in the training set. Furthermore, there are concerns about the applicability domain of the model for the specific prediction: the half-lives of structural analogues provided in the QPRF are all underestimated. Moreover, ECHA also notes that they all have exactly the same experimental value. In addition, the structures of the analogues do not cover the complexity of the target (two oxygen atoms in the target vs. one oxygen for all analogues).

Consequently, the information gap is valid and it is necessary to provide the requested information.

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

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: Aerobic mineralisation in surface water – simulation biodegradation test (test method: EU C.25./OECD TG 309), at 12^{0}C.

9. Identification of degradation products (Annex IX, 9.2.3.)

The identification of the degradation products is a standard information requirement according to column 1, Section 9.2.3. of Annex IX of the REACH Regulation. Column 2 of Section 9.2.3. of Annex IX further states that the study does not need to be conducted if the substance is readily biodegradable.

You have provided a QSAR prediction for simulation testing in surface water but have not provided adequate information on the identification, stability, behaviour, and quantity of the degradation products relative to the parent compound. Additionally, there is no adaptation provided by you to cover this endpoint.

In your comments to the draft decision, it is stated: "The IUCLID dossier has been updated (submission number : [redacted]) with the following element : Based on the general hydrolysis pathway of acetals under acidic circumstances, ethylal is predicted to hydrolyse into ethanol and formaldehyde (as discussed in Toxicokinetic section_[redacted])."

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. All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation.

Irrespective of whether the newly provided information may be sufficient to meet the information requirement addressed in this decision, ECHA can already point out the following: This information could not be found in the updated dossier. The reference/summary to the published literature is not sufficiently detailed to assess it and other degradation products might occur in the natural environment than the ones produced via hydrolysis in acidic circumstances.

ECHA hence considers that the information provided on the degradation products in the technical registration dossier or in the Chemical Safety Report is not sufficient to demonstrate absence of the need for further information on the relevant transformation and/or degradation products.
Consequently, the information gap is valid and it is necessary to provide the requested information.

Regarding appropriate and suitable test method, the methods to be applied will have to be substance specific. When analytically possible, identification, stability, behaviour, molar quantity of metabolites relative to the parent compound should be evaluated. In addition degradation half-life, log Kow and potential toxicity of the metabolite may be investigated. You may obtain this information from the simulation study also requested in this decision, or by some other measure such as modelling. You will need to provide a scientifically valid justification for the chosen method.

Therefore, pursuant to Article 41(1)(a) and (b) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Identification of the degradation products using an appropriate and suitable test method, as explained above in this section.

Before conducting the above test you are advised to consult the ECHA Guidance on information requirements and chemical safety assessment (version 1.2, November 2012), Chapter ECHA Guidance on information requirements and chemical safety assessment Sections R.7.9.2.3 and R.7.9.4. These guidance documents explain that the data on degradation products is only required if information on the degradation products following primary degradation is required in order to complete the chemical safety assessment. Section R.7.9.4. further states that when a substance is not fully degraded or mineralised, degradation products may be determined by chemical analysis.

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 02 October 2015.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

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

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

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment.

ECHA received proposal(s) for amendment and did not modify the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-50 meeting and ECHA took the decision according to Article 51(6) 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 carrying out the test(s) required by the present decision it is important to ensure that the particular sample of substance tested 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. If the registration of the substance covers different grades, the sample used for the new test(s) must be suitable to assess these. Furthermore, 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.