ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 30 November 2016

Addressee: [redacted]

Decision number: CCH-D-2114348441-54-01/F
Substance name: 1,1'-[methylenebis(oxy)]dibutane
EC number: 219-909-0
CAS number: 2568-90-3
Registration number: [redacted]
Submission number: [redacted]
Submission date: 11.04.2014
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. **Vapour pressure (Annex VII, Section 7.5; test method: EU A.4/OECD TG 104) of the registered substance;**

2. **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**

3. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3; test method: EU B.17/OECD TG 476) with the registered substance provided that the study requested under point 2 above has negative results;**

4. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2; test method: EU B.26/OECD TG 408) in rats with the registered substance;**

5. **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;**

6. **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;**

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

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

9. **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;**

10. **Identification of degradation products (Annex IX, 9.2.3.) using an appropriate and suitable test method, as explained in section 10 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 **9 December 2019**. You shall also update the chemical safety report, where relevant.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. 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

Grouping of substances and read-across approach

You have proposed to cover the standard information requirements for 1,1'-[methylenebis(oxy)]dibutane (hereafter referred to as "butylal") for

- *in vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2);*
- *in vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.);*
- *sub-chronic toxicity study (90-day; Annex IX, Section 8.6.2.) and*
- *for the 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 availabilities of their experimental studies the substances were employed as source or target substances.

Properties obtained in 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 substances. In the current decision ECHA limits the analysis to the predictions proposed for butylal (i.e. the target substance).

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

For the genotoxic properties of butylal, investigated in the *in vitro* cytogenicity study in mammalian cells methylal (CAS no 109-87-5) was used as a source substances and in the *in vitro* gene mutation study in mammalian cells, the source substances ethylal (CAS 462-95-3) and 1,3-dioxolane (CAS no 646-06-0; hereafter referred to as "dioxolane") were employed.

For the studies investigating the repeated dose toxicity of the target substance the source substances methylal and dioxolane were employed, and for the pre-natal developmental toxicity the source substance dioxolane was used.

ECHA understands that the grouping approach is based on the similarity in the chemical structure of the above mentioned substances i.e. 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 vitro* gene mutation study in mammalian cells 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. butylal [...]
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. [...] butylal, 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 endpoints 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. [...] butylal, 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, propylal, butylal, 2,5,7,10-tetraoxaundecane and 2-ethylhexylal, 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 your dossier, Submission number: [redacted], you have provided the following information:

You have provided the read-across justification as attachments to the IUCLID file. Separate read-across justification documents have been submitted for the "*genotoxicity super endpoint*" (i.e. justifying predictions for the *in vitro* cytogenicity study in mammalian cells and the *in vitro* gene mutation study in mammalian cells) 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 predictions and comparison of selected physico chemical properties) for the "*genotoxicity super endpoint*" and for the "*toxicity super endpoint*", respectively.

The provided data matrices contain the results of the available experimental studies on the source substances, supporting QSAR predictions and the applied read-across for the registered substance. Experimental test results on the source substances for genotoxicity, acute dose toxicity, repeated dose toxicity (28 and 90 days via inhalation) and prenatal 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 and structural dysmorphogensis are included in the above mentioned justification documents.

In the technical dossier and CSR you have provided oral and dermal acute toxicity, skin and eye irritation, skin sensitisation and Ames test 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 i.e. 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 bound. 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, ethylal and butylal is properly described. They possess differences in the length of the linear alkyl chains having methyl, ethyl and butyl 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 butylal (and 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 target and source.

Given the structural differences between dioxolane and butylal, ECHA considers that there is not an adequate basis for predicting the properties of butylal from the data of dioxolane.

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 prenatal 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. 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 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 the 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 butylal 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 butylal.

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 model or similar compounds were not represented in the training set. This is also relevant for the ecotoxicological endpoints. In addition you assigned the reliability of these predictions as *"very little reliable"*.

You also used 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 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 which 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 prenatal developmental toxicity only the estrogen receptor binding and DART scheme profiler are related to the reproductive/developmental effects. ECHA notes, due to the shortcomings explained above, the presented QSAR data cannot be used to justify the prediction of toxicological properties related to human health.

ECHA further notes that the additional QSAR predictions on developmental toxicity, i.e. structural dysmorphogensis in different species by Leadscope have been excluded from ECHA's assessment due to their low reliability and/or existing waiver you provided 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 are not adequate for supporting the proposed similarity in the mechanism of action and to justify the predictions of toxicological properties related to human health.

Reliability and adequacy of the source studies

ECHA observes that in the technical dossier of the target substance you have not submitted robust study summaries of any of the available experimental data on the source substances. ECHA notes that currently the source studies which investigate the properties to be read-across to the registered substance cannot be assessed. Therefore it cannot be verified in this dossier whether the study design is adequate and reliable for the purpose of the prediction, whether the test material used represents the source substance as described in the justification documents, and whether the results are adequate for the purpose of classification and labelling and/or risk assessment.

In the absence of this information, an independent assessment on whether the source studies meet the REACH requirements in terms of reliability and adequacy as requested for any key study is not possible.

On this basis alone (lack of robust study summaries of the experimental data on the source substances) the dossier is incompliant for all endpoints to which you apply a read-across approach and there is not an adequate basis for predicting the properties of butylal from the data of the source substances.

Additional considerations concerning genotoxicity

For the endpoint *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study 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 endpoint *in vitro* gene mutation in mammalian cells test you have provided negative results from an OECD 476 test conducted with dioxolane and results from a non GLP OECD 476 test conducted with ethylal, which were negative without and positive with metabolic activation. You have stated that QSAR predictions for this endpoint are "*very little reliable*".

For the *in vivo* micronucleus test you have provided negative results from an OECD 474 test conducted with methylal.

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

ECHA observes that positive Ames test results for the source substance methylal exists, as cited by EFSA (ref.: EFSA Journal 2011; 9(10):2312) but not mentioned in the butylal dossier. Given that the Ames test results for butylal were negative this indicates an inconsistency in the mode of action between methylal and butylal.

As explained under "Structural similarity and dissimilarity" dioxolane has a cyclic chemical structure which structural differences lead to the conclusison that there is not an adequate basis for predicting the properties of butylal from the data of dioxolane.

In addition, ECHA observes that reliable QSAR predictions for the genotoxicity endpoint gave positive alerts for the micronucleus test for dioxolane, and therefore dioxolane "*might exhibit a different genotoxic mechanism of action with respect to the targets [...] butylal*". On the other hand there is no positive alert for methylal, ethylal and butylal in similar QSAR predictions.

ECHA notes that the above statement contradicts with your explanation that sources and target possess a common mechanism of action:

"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. [...] butylal, 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 endpoints and in terms of mechanism of actions."

Hence, it cannot be confirmed that dioxolane would have a similar behaviour to the target or the other source substances with regard to the mechanism of action relevant for genotoxicity.

Furthermore, ECHA observes that OECD 476 test results on ethylal are negative without and positive with metabolic activation, whereas results of the same test on dioxolane are all negative. This indicates an inconsistency in the mode of action between ethylal and dioxolane.

In summary, based on these findings, it cannot be confirmed that target and source substances would have a similar or regular pattern with regard to the mechanism of action relevant for genotoxicity.

Furthermore, you propose that on the ground of the OECD 476 test results on ethylal (negative without and positive with metabolic activation) the *"genotoxicity on mouse lymphoma of butylal would be predicted negative (without activation) and positive (with activation) in the worst case scenario".* However instead of the worst case scenario you have used a *"weighted mode formalism"*, which is considered by you to be *"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.

ECHA also observes, that you have not submitted robust study summaries of the experimental data on the source substances.

For all of the reasons set out above, ECHA considers that there is not an adequate basis for predicting the properties of butylal from the data of the source substances.

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 butylal 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 butylal, 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, i.e. the worst case scenario, you have used the 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. For the registered substance, no information is available which would allow a comparison of its toxicity profile after repeated administration with the source substances. In the absence of such information a similar or regular pattern with regard to predictions for repeated dose toxicity cannot be established.

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 butylal.

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

In summary, 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 properties of butylal 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 ($NOAEL_{dev}$ 31814 and $NOAEL_{maternal}$ 6174 mg/m^3) via inhalation and dioxolane ($NOAEL_{maternal\ and\ dev}$ 250 mg/kg bw/day and $NOAEL_{dev}$140 mg/kg bw/day from non GLP studies) via oral route.

ECHA observes that you have chosen dioxolane as an analogue substance based on the route of exposure: *"since the oral route is relevant for [...] and butylal [...], the dioxolane data were read-across to [...] and butylal"*. 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.

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

ECHA further notes that the additional QSAR predictions on developmental toxicity been excluded from ECHA's assessment due to their low reliability and/or existing waiver you provided in the technical dossier as explained above.

ECHA also observes, that you have not submitted robust study summaries of the experimental data on the source substance dioxolane.

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

In summary, given the lack of robust study summaries of the experimental data on the source substance, the differences in the structure and 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 butylal from the source substance, dioxolane.

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

ECHA considers that, for the reasons presented above, you have failed to explain as to how and why, in qualitative and quantitative terms, the (eco)toxicological properties of the registered substance can be accurately predicted by using the available information from the proposed source substances. As explained above, there is a 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.

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 vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.); the 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 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 that are based on Annex XI, 1.5.

In your comments to the draft decision, under point 3 and 4, 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 *in vitro* gene mutation study in mammalian cells and the repeated dose toxicity (90d) 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-across 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 butylal (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 routes of administration (*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 *"Ecetoc Publications, 2004"* provides more information on the *"metabolism of degradation products of butylal"*. ECHA observes that the mentioned study (JACC 041, 2004) is an assessment report on the substance n-butanol. ECHA notes that this document does not contain any information on the toxickokinetic properties of butylal. You postulate in your statement document related to toxicokinetic similarity ([redacted]) that butylal will hydrolyse into n-butanol and formaldehyde. ECHA observes that none of the submitted supporting information provides evidence on the existence, the nature and extend of the hydrolysis of butylal, the formation of n-butanol as a postulated degradation products of butylal.

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 butylal (the target substance).

Moreover, in your statement related to toxicokinetic similarity ([redacted] you draw the same conclusion as the above mentioned study: *"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, the you note in the same place: *"that the in silico analysis of the ADME properties and toxicokinetic (TK) behavior of the 2 acetals (methylal, butylal) 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 butylal from the data of the source substance metylal.
Additional consideration concerning the genotoxicity and the sub-chronic toxicity (90 day), are outlined in the relevant sections (Section 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 vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.); the 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 that are based on Annex XI, 1.5.

1. Vapour pressure (Annex VII, Section 7.5.)

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

"Vapour pressure" is a standard information requirement as laid down in Annex VII, Section 7.5 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.

ECHA observes, from the reporting in the endpoint study record, that you have performed the experiment, flagged as key study, according to an "Internal guideline of [redacted]".

You did not justify that the method used is equivalent to standard EU/OECD test methods and reporting does not allow ECHA to assess. Moreover, you state that you have used the dynamic method. ECHA observes that you did not perform the study according to the guidelines (EU A.4./OECD TG 104.), which recommend to perform this method in the range of $2x10^3$ Pa to 10^5 Pa. However, you performed the method in the range of 10^2 to 10^5 Pa.

Under Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA. ECHA concludes that you did not follow any test method recognised by the Commission or ECHA and, furthermore, did not provide information to justify that the used method would be equivalent.

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.

In your comments you have indicated that you provided an updated IUCLID dossier with new information, after you have received this draft decision, addressing the deficiencies identified by ECHA.

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 have indicated that the key study was performed accordingly to EU A.4 test method, and have justified the deviation for the selected test range. You have further provided the "log P versus 1/T" curve used to extrapolate the vapour pressure at 20 °C.

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: Vapour pressure (test method: EU A.4./OECD TG 104).

2. 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 an *in vitro* cytogenicity study results in mammalian cells (OECD TG 473) with the analogue substance methylal (CAS no 109-87-5) and QSAR predictions. 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.

For these reasons 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.

In your comments to the draft decision you agreed to conduct the requested study.

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).

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

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 gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained. ECHA notes that the registration dossier contains negative results for the Annex VII, Section 8.4.1. information requirements and does not contain an acceptable study record for Annex VIII, Section 8.4.2. Therefore, adequate information on *in vitro* gene mutation in mammalian cells needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing an *in vitro* mammalian cell gene mutation test (OECD TG 476) results with the analogue substance 1,3-dioxolane (CAS no 646-06-0) and QSAR predictions. 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.

In your comments you have indicated that you provided an updated IUCLID dossier with the following elements: 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. Based on the provided information ECHA understands that in your updated read-cross approach you propose to use methylal as a source substance for this endpoint.

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 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.

In addition, ECHA observes that in your comments you intend *"supporting the absence of positive alert with methylal"* by providing further results of genotoxicity tests performed with methylal in an *in vitro* OECD 476 ([redacted]) and *in vivo* OECD 474 ([redacted]) studies. ECHA notes that due to the reason that your proposed adaptation (*i.e.* your updated read-across approach) is rejected these studies cannot be taken into consideration as supporting evidence and/or to determine the necessity to perform the *in vitro* mammalian cell gene mutation test. Thus, ECHA notes that the necessity to perform the *in vitro* mammalian cell gene mutation test depends only on the result of the genotoxicity study as requested under section 2 with the registered substance (*in vitro* cytogenicity study in mammalian cells or *in vitro* mammalian cell micronucleus study) and which you have agreed to perform with the registered substance.

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: *In vitro* mammalian cell gene mutation test (test method: EU B.17./OECD TG 476) provided that the study requested under 2 has negative results.

4. Sub-chronic toxicity study (90-day), oral 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 study results with the analogue substances methylal (CAS no 109-87-5) and 1,3-dioxolane (CAS no 646-06-0) and QSAR predictions. 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.

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

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA Guidance on information requirements and chemical safety assessment (version 4.0, July 2015) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. More specifically, even though the information indicates that human exposure to the registered substance by the inhalation route is likely, there is no concern for severe local effects following inhalation exposure. Furthermore, ECHA points out that no repeated dose toxicity study by the oral route is available. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

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

In your comments you have indicated that you provided an updated IUCLID dossier, where you explain that your read across approach (Pavan, 2016) has been updated with 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. 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 the sub-chronic toxicity study (90 day) endpoint.

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 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.

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 butylal, supporting the similarity of toxicokinetic behavious 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 repeated dose toxicity - 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." 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: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats.

5. 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. A pre-natal developmental read across is available.*

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 the 90-d study read-across. "*

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 argument, 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 under section 8.7.3 of Annex IX. 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 422/421, 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: *"this study can be waived 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 TG 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 consideration

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

6. 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 studies study results with the analogue substance 1,3-dioxolane (CAS 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.

Therefore, 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 consideration, 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 you agreed to conduct the requested study.

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.

7. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

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.

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

Column 2 of Annex IX, Section 9.1. specifies that long-term aquatic toxicity testing shall be proposed by the Registrant if the chemical safety assessment according to Annex I indicates the need to investigate further effects on aquatic organisms. The choice of the appropriate test(s) will depend on the results of the chemical safety assessment.

You have provided an ECOSAR (v1.11) predicted NOEC value of 1.975 mg/L and reported that the "*QSAR has been performed with both isomers of glycerol formal (showing the same predicted values)*". This value was also used for the PNEC aquatic derivation.
ECHA notes that the proposed prediction, as indicated by you, refers to a completely different substance (glycerol formal) than the registered one. Secondly, the ECOSAR neutral organic equation for *Daphnia* chronic toxicity is only based on few experimental results and none of the substances in the training set are close analogues to the substance pursuant to the current decision. Therefore, the substance is not considered to fall into the applicability domain of the model.

In your comments you have indicated that you provided an updated IUCLID dossier with the following elements: "*The correct name of the substance has been added (butylal instead of glycerol formal) whereas the prediction was related to butylal. The prediction is provided for information as PNEC has been generated from acute aquatic toxicity test. A laboratory test is therefore no-longer required to feed the chemical safety assessment*".

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 ECOSAR neutral organic equation for *daphnia* chronic toxicity is only based on few experimental results and none of the substances in the training set are close analogues to the registered substance. This raises concerns about the applicability domain of the model.

Thus, the information provided on this endpoint for the registered substance in the technical dossier as per Submission number: [redacted] and the registrants comments on the draft decision does not meet the information requirement. 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: *Daphnia magna* reproduction test (test method: EU C.20./OECD TG 211).

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

"Long-term toxicity testing on fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. of the REACH Regulation. Adequate information on Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.), or Fish, short-term toxicity test on embryo and sac-fry stages (Annex IX, 9.1.6.2.), or Fish, juvenile growth test (Annex IX, 9.1.6.3.) needs to be present in the technical dossier for the registered substance to meet this information requirement.

Column 2 of Annex IX, Section 9.1. specifies that long-term aquatic toxicity testing shall be proposed by the Registrant if the chemical safety assessment according to Annex I indicates the need to investigate further effects on aquatic organisms. The choice of the appropriate test(s) will depend on the results of the chemical safety assessment.

You have provided an ECOSAR (v1.11) predicted NOEC value of 2.903 mg/L and reported that the "*QSAR has been performed with both isomers of glycerol formal (showing the same predicted values)*".

For the reasons explained in the previous sub-section 7, 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.

Regarding the long-term toxicity testing on fish pursuant to Annex IX, section 9.1.6.1, ECHA considers that the FELS toxicity test according to OECD TG 210 is the most sensitive of the standard fish tests available as it covers several life stages of the fish from the newly fertilised egg, through hatch to early stages of growth and should therefore be used (see ECHA Guidance on information requirements and chemic al safety assessment (version 2.0, November 2014), Chapter R7b, Figure R.7.8-4 page 26). The test method OECD TG 210 is also the only suitable test currently available for examining the potential toxic effects of bioaccumulation (ECHA Guidance R7b, version 2.0, November 2014, p. 26). For these reasons, ECHA considers the FELS toxicity test using the test method OECD TG 210 as appropriate and suitable.

In your comments you have indicated that you provided an updated IUCLID dossier with the following elements: "The correct name of the substance has been added (butylal instead of glycerol formal) whereas the prediction was related to butylal. The prediction is provided for information as PNEC has been generated from acute aquatic toxicity test. A laboratory test is therefore no-longer required to feed the chemical safety assessment".

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 ECOSAR neutral organic equation for fish chronic toxicity is only based on few experimental results and none of the substances in the training set are close analogues to the registered substance. This raises concerns about the applicability domain of the model.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Fish, early-life stage (FELS) toxicity test (test method: OECD TG 210).

Before conducting any of the tests mentioned above in points 7 and 8, you shall consult the ECHA Guidance on information requirements and chemical safety assessment (version 2.0, November 2014), Chapter R7b, Section R.7.8.5 to determine the sequence in which the aquatic long-term toxicity tests are to be conducted and the necessity to conduct long-term toxicity testing on fish.

According to ECHA Guidance on information requirements and chemical safety assessment (version 2.0, November 2014), Chapter R7b (Section R.7.8.5., including Figure R.7.8-4), if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially more sensitive, long-term studies may be required on both. In such case, according to the integrated testing strategy, the Daphnia study is to be conducted first. If based on the results of the long-term Daphnia study and the application of a relevant assessment factor, no risks are observed (PEC/PNEC<1), no long-term fish testing may need to be conducted. However, if a risk is indicated, the long-term fish study needs to be conducted.

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

"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 129 hours and have concluded, in the PBT assessment, that the substance is not considered to fulfil the P criterion. You also provided a 1999 screening study according to OECD Guideline 301 F (Ready Biodegradability: Manometric Respirometry Test) that resulted ina 40-50% degradation (based on O_2 consumption) after 34 days.

ECHA notes that 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, 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.

Thus, 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 your comments 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 registered substance (two oxygen atoms in the target vs. one oxygen for all analogues).

In the present dossier Submission number: [redacted] and the Registrants comments to the draft decision, ECHA notes that the information on this endpoint is not available. The technical dossier Submission number: [redacted] does not either contain 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 for this standard information requirement.

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.

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.

10. 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 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: However, 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. Therefore, this statement is not sufficient to fulfil the information requirement for the identification of the degradation products.

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.

Regarding appropriate and suitable test method, the methods 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. 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, the Registrant is 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 30 September 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. 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.