ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 09 July 2018

Addressee: [redacted]

Decision number: CCH-D-2114428300-65-01/F
Substance name: 1-phenylethyl acetate
EC number: 202-288-5
CAS number: 93-92-5
Registration number: [redacted]
Submission number: [redacted]
Submission date: 09/06/2017
Registered tonnage band: 100-1000

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:[1]

1. **In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method: OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2, test method: OECD TG 487) with the registered substance;**

2. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance, provided that the study requested under 1. has negative results;**

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

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

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH Regulation. To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **16 January 2020**. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

[1] No testing for endpoints listed in Annexes IX or X to the REACH Regulation may be started or performed at this moment: A decision only becomes legally effective and binding for you after it has been adopted according to Article 51 of the REACH Regulation. ECHA will take the decision either after the date it has become clear that Member State competent authorities have not made any proposals to amend the draft decision or, where proposals to amend it have been made, after the date the Member State Committee reached a unanimous agreement on the draft decision.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[2] by Kevin Pollard, Head of Unit, Evaluation E1

[2] 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

TOXICOLOGICAL INFORMATION

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

Your registration dossier contains for the endpoints *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study (Annex VIII, Section 8.4.2.), *in vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.), sub-chronic toxicity study (Annex IX, Section 8.6.2.) ,screening for reproductive/developmental toxicity study (Annex IX, 8.7.1.) and pre-natal developmental toxicity study (Annex IX, 8.7.2) adaptation arguments in form of a grouping and read-across approach under Annex XI, Section 1.5. of the REACH Regulation. ECHA has considered first the scientific and regulatory validity of your read-across approach in general before assessing the individual endpoints (sections 1 to 4).

Grouping of substances and read-across approach

You have sought to adapt the information requirements for *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study (Annex VIII, Section 8.4.2.), *in vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.), sub-chronic toxicity study (Annex IX, Section 8.6.2.), screening for reproductive/developmental toxicity study (Annex IX, Section 8.7.1.) and pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) by applying a read-across approach in accordance with Annex XI, Section 1.5. According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

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

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus, physicochemical and degradation properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical and degradation properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis- (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

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

A. Read-across hypothesis

You consider to achieve compliance with the REACH information requirements for the registered substance 1-phenylethyl acetate (EC no. 202-288-5) using data of the structurally similar substance benzyl acetate (EC no 205-399-7) (hereafter the 'source substance').

You have provided a read-across documentation as a separate attachment for each endpoint in the registration dossier. Furthermore you have provided QSAR predictions under the respective IUCLID sections as well as in the CSR. In these documents information from studies with substances showing structural similarities with the registered substance has been presented. However, no study reports for these substances were submitted.

You use the following arguments to support the prediction of properties of the registered substance from data for source substances within the group:

"*This read-across is based on the hypothesis that the target substance and source substance have the same expected mode of action and similar physicochemical properties relevant for the read-across endpoints.*"

As regards the substance identity, chemical structure and toxicological profile of the source and target substances you state:
"*The target substance and the source substance(s) do not contain any impurities present at ≥ 1%. The purity of the test item is 98.8% for gardenol and >99% for benzyl acetate as presented within the respective REACH registration dossiers.*"

*"The target substance and the source substance have been characterised in this table using the categories and databases present in the OECD [Q]SAR Toolbox. From the profiling provided (**Table 2**), it can be seen that the 2 substances share structural similarities and also mechanistic actions which are both general and endpoint specific."*
"The OECD toolbox predicts all substances to be of low toxicity according to Cramer classes and both substances show no alerts according to DART Scheme v1.0."
As regards the metabolism of the source and target you conclude that:
"The target and source substance are structurally similar acetates which are expected to predominantly form acetic acid and benzoic acid after metabolism. The primary route of metabolism for both substances is expected to be via rapid initial ester hydrolysis followed by aliphatic C-oxidation. This is supported by the most probable route of metabolism prediction of TIMES v.2.27.17 (rat in vivo model)."
"The experimental data presented indicates that the toxicity of the parent substances and the metabolites formed are similar based on the repeated dose toxicity and the reproductive study results. This therefore supports the use of read-across to benzyl acetate in an analogue approach, or as part of a larger category approach."
As regards genotoxicity of the target substance mechanistic profiling is presented:
"The target gardenol and 8 of the potential source substance have a profiler alert for "potential" DNA binding via the OECD profiler (Michael addition >> P450 Mediated Activation to Quinones and Quinone-type Chemicals >> Arenes). This is consistent with the main source substances (benzyl acetate). In addition, the target and the rest of the category members do not have alerts for carcinogenicity or DNA alerts for Ames by OASIS v.1.4. Considering that all category members have negative bacterial reverse mutation data, it has been shown that the bacterial mutation endpoint has been covered for all 11 category members and been shown not to be an issue for gardenol."

As regards reproductive toxicity profile of the target substance mechanistic profiling is presented:
*"In addition, **Table 4** provides additional potential source substances for read-across based on mechanistic profiling in the OECD [Q]SAR Toolbox.*

There is no evidence from this additional supporting data that any of the substances presented in the data matrix may be a concern for reproductive or developmental toxicity based on the available toxicology data, and further support that this group of substances have a low order of reproductive toxicity, that does not vary by the addition of the methyl group in the target substance..." and you conclude that *"Strong evidence of lack of reproductive and developmental toxicity is shown across all 14 source substances..."* used for the modelling.
Based on the information above you conclude that:
"The overall assessment of the experimental Genetic Toxicology data indicates that gardenol and this group of substances do not cause any concern for mutagenicity."
"The target substance and the source substance are expected to follow the same metabolic pathway and act via the same mode of action for higher tier studies for in vivo reproductive and developmental toxicity."
You also provide summaries of studies for the source substance which ECHA has evaluated under the respective endpoints in Sections 1 to 5 of Annex I.
As an integral part of this prediction, you propose that the source and registered substance(s) have similar properties for the above-mentioned information requirements.
ECHA considers that this information is your read-across hypothesis.

B. ECHA's evaluation and conclusions

Your proposed adaptation argument is that the structural similarity between the source and registered substance is a sufficient basis for predicting the properties of the registered substance. Structural similarity is a prerequisite for applying the grouping and read-across approach. However structural similarity does not necessarily lead to predictable or similar human health properties. You have not established why a prediction for a human health property is reliable. Thus structural similarity per se is not sufficient to enable the prediction of human health properties of a substance.

You further argue that the source and the target substances follow a similar metabolic pattern and that the organism will be exposed to similar compounds. However, even if data on the metabolism of the source substance has been provided, and the prediction of the proposed metabolic pathways of the source and the target substances is supported by *in situ* modelling, such considerations remain too theoretical as there is no experimental supporting documentation to verify the metabolic pattern or rate of the target substance. Furthermore, ECHA notes that the additional methyl group of the target substance predisposes it to have metabolites different from benzoic acid, which are not addressed in the read-across justification.

As regards genotoxicity and toxicity to reproduction/fertility no experimental evidence has been given for the target substance. Hence, it is not possible to verify that the information provided for the target substance, nor the QSAR predictions for these endpoints, can be used as a reliable basis to predict the outcome of an *in vitro* cytogenicity study in mammalian cells, *in vitro* micronucleus study, or *in vitro* gene mutation study in mammalian cells. Furthermore, reproductive toxicity of the target substance cannot be predicted from the submitted information. Some detailed information related to the evaluation of the QSAR predictions and why they are not considered to fulfil the provisions of Annex XI, Section 1.3 are given under the respective endpoints in Appendix 1.

As regards repeated dose toxicity there is a sub-chronic toxicity study available with the registered substance that could potentially have been used to compare repeated dose toxicity of the source and the target substances. However, no such comparison has been made.

On that basis, the requirement of Annex XI, Section 1.5., that human health effects may be predicted from data for reference substance(s) within the group, has not been met. ECHA notes that there are specific considerations for the individual endpoints which also result in a failure to meet the requirement of Annex XI, Section 1.5., and these are set out under the endpoint concerned.

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

ECHA notes that in your comments on the draft decision you have not provided further experimental information to support the proposed read-across adaptation. ECHA considers that QSAR predictions may provide indicative and supporting evidence, which may contribute to the read-across documentation, but are generally insufficient as standalone information in most cases (RAAF 2017, ECHA). In this case, the overall read-across documentation and justification remain insufficient as explained above.

Concerning your specific comments on metabolism of source and target substances, ECHA finds that there is a structural difference between the source and target substances, which leads to a difference between the metabolites of these two substances. For benzyl acetate, further dehydrogenase metabolism to benzoic acid is likely, whereas the target substance will hydrolyze to a secondary aromatic alcohol, which can be metabolized to a ketone. ECHA recognizes that there is no experimental data on metabolism, and there are uncertainties involved in the metabolic steps given above.

Finally, ECHA concludes that you have not demonstrated that the metabolites of the target and sources substances are sufficiently similar in their properties, and that the data on metabolites allows the prediction of the toxicity of the target substance from the available information on the source substances.

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

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

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing two study records for *in vitro* mammalian chromosome aberration tests (OECD TG 473) with the analogue substance benzyl acetate (EC no 205-399-7). You have also provided one mammalian bone marrow chromosome aberration study (OECD TG 475) and two mammalian erythrocyte micronucleus tests (OECD TG 474) with the analogue substance benzyl acetate (EC no 205-399-7).

You have also provided QSAR Toolbox predictions for the following studies: OECD TG 473, OECD TG 474, and OECD TG 475.

However, as explained above in section "*Grouping of substances and read-across approach*", your adaptation of the information requirement is rejected.

ECHA has furthermore evaluated your QSAR predictions in accordance with Annex XI, Section 1.3 of the REACH Regulation.

As regards the QSAR Toolbox predictions for this endpoint the endpoint study record referring to OECD TG 473 contains a report for a prediction for OECD TG 474. ECHA has evaluated the prediction for this study, which is based on a read-across from five different chemicals that were grouped into a category. This category is generated on the basis of structural similarity and similar mode of action, as highlighted by the QSAR Toolbox profilers related to mutagenicity.

The category seems coherent from the perspective of the Toolbox alerts, but from all of the category members, only phenylacetate contains the ester functionality. Based on the information provided, this substance will metabolise quickly via ester hydrolysis, but the read-across does not consider whether the target substance will follow the same pathway and, if it does, if the degradation products of the target substance can cause effects. In particular, one of the predicted degradation products of the registered substance is 1-phenylethanol, which is not observed for the very close analogue phenylacetate, and for which the Toolbox contains two experimental values of "positive" in an in vitro mammalian chromosome aberration test and a mammalian cell gene mutation assay (Mutation Research 584, 2005, p. 1-256). Therefore the read-across cannot be accepted.

As regards the QSAR Toolbox prediction for OECD TG 475, ECHA considers that the category seems coherent from the perspective of the Toolbox alerts, but that the members are only structurally related to the target substance by the presence of a benzene ring, and none of the member substances contain an ester. In addition, most of the substances chosen for the category are UVCBs, for which only a representative structure is available adding up to the uncertainty of the prediction.

Taken together, ECHA considers that there is not a reliable basis for predicting the properties of the registered substance "from data for reference substance(s) within the group by interpolation to other substances in the group", as required by Annex XI, 1.5. In consequence, the predictions are not adequate for the purpose of classification and labelling and/or risk assessment as required by Annex XI, Section 1.3. Hence, the predictions are rejected.

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

ECHA notes that in your comments on the draft decision you have not provided further experimental information to support the proposed read-across adaptation for this endpoint. ECHA considers that QSAR predictions may provide indicative evidence, which may contribute to the read-across documentation, but are generally insufficient as standalone information in most cases (RAAF 2017, ECHA). In this case, a positive study included in the QSAR Toolbox contradicts with the otherwise negative evidence on genotoxicity.

Concerning the cell line used to test 1-phenylethanol, ECHA considers that testing with a sub-optimal cell line does not as such invalidate the results of the test. Furthermore, the study has passed the peer review of a prominent scientific journal and should be considered to be an indicative evidence of genotoxicity. Consequently, the category proposed by you is not supported by the genotoxicity information, because the results are inconsistent. Therefore, further testing is needed to clarify the concern.

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

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

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

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

ECHA notes that the registration dossier does not contain appropriate study records for these information requirements. 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 provided that the studies requested under section 1 has negative results.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study records for two *in vitro* mammalian cell gene mutation tests (OECD TG 476) with the analogue substance benzyl acetate (EC no 205-399-7).

You have also provided a QSAR Toolbox prediction for the following study: OECD TG 490.

However, as explained above in section "*Grouping of substances and read-across approach*", your adaptation of the information requirement is rejected.

ECHA has furthermore evaluated your QSAR predictions in accordance with Annex XI, Section 1.3 of the REACH Regulation.

The QSAR Toolbox prediction is based on a read-across from five different chemicals that were grouped into a category. This category is generated on the basis of structural similarity and similar mode of action, as highlighted by the QSAR Toolbox profilers related to mutagenicity.

The category seems coherent from the perspective of the Toolbox alerts, but they are only structurally related to the target substance by the presence of a benzene ring, and none of them contains an ester. The differences in the metabolism of the category members and the target substance have not been addressed e.g., the closest analogue considered is toluene, which metabolises to benzyl alcohol and not to 1-phenylethanol, as the registered substance does.

As mentioned in Section 1 above, ECHA found two experimental values of "positive" in an in vitro mammalian chromosome aberration test and a mammalian cell gene mutation assay (Mutation Research 584, 2005, p. 1-256) in the QSAR Toolbox for the predicted degradation product for 1-phenylethanol. In addition, some of the substances chosen for the category are UVCBs, for which only a representative structure is available, adding up to the uncertainty of the prediction. These considerations have not been addressed or assessed in your read-across justification.

For these reasons, ECHA considers that there is not a reliable basis for predicting the properties of the registered substance "from data for reference substance(s) within the group by interpolation to other substances in the group", as required by Annex XI, 1.5. In consequence, the predictions are not adequate for the purpose of classification and labelling and/or risk assessment as required by Annex XI, Section 1.3. Hence, the predictions are rejected.

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

ECHA notes that in your comments on the draft decision you have not provided further experimental information to support the proposed read-across adaptation. ECHA considers that QSAR predictions may provide indicative evidence, which may contribute to the read-across documentation, but are generally insufficient as standalone information in most cases (RAAF 2017, ECHA). In this case, a study included in the QSAR Toolbox demonstrates contradicting/ambiguouss evidence on genotoxicity.

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

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

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

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

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

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing two study records with an analogue substance:

- End-point study record 1:- Sub-chronic toxicity study 13 weeks**:** rat, oral (similar or equivalent to OECD TG 408; GLP not specified) with source substance benzyl acetate (EC no 205-399-7), Morrissey et al., 1988 (publication and study report), reliability 2.

- End-point study record 2:- Sub-chronic toxicity study 13 weeks: mouse, oral (similar or equivalent to OECD TG 408; GLP not specified) with source substance benzyl acetate (EC no 205-399-7), Morrissey et al., 1988 (publication and study report), reliability 2.

You have also provided two QSAR Toolbox predictions for the following studies: OECD TG 421, OECD TG 422, OECD TG 415, and OECD TG 416.

As explained above in section "*Grouping of substances and read-across approach*", your adaptation of the information requirement is rejected. In addition ECHA notes that it is unclear whether the studies are GLP, which is required under Article 13(4) of the REACH Regulation, and the studies submitted do not provide the information required by Annex X, Section 8.7.2., because the sub-chronic toxicity studies do not include mating of the animals, and hence, reproductive outcome is not covered.

You have furthermore sought to adapt this information requirement by providing the following waiver: "I*n accordance with Annex VIII section 8.7.1 column 2 adaptation this study does not need to be conducted if a two-generation reproductive toxicity study is available. A combined one-generation and a two-generation reproductive toxicity [Q]SAR on the structural similar analogues as defined within within the OECD [Q]SAR toolbox based on DART scheme v.1.0., Organic functional groups, Lipinski Rule OASIS, Structural similarity. Chemical elements, Test guideline, Test type, Test organisims (species), Route of administration, Reliability and Substance type. See section 7.8.1 of IUCLID. Read across to this substance is justified based on similarity in structure and biological activity."*
You refer in your adaptation to Annex VIII, Section 8.7.1., Column 2 of the REACH Regulation and conclude that according to this provision a screening study for reproduction does not need to be performed if a two-generation reproductive toxicity study is available.

ECHA agrees that a two-generation study according to OECD TG 416 may fulfil the information requirements for this endpoint. However, such study has not been included in your technical dossier.

ECHA has furthermore evaluated your QSAR predictions in accordance with Annex XI, Section 1.3 of the REACH Regulation.

As regard the QSAR Toolbox predictions for toxicity to reproduction, ECHA notes that the relevant section of Column 2 does not refer to QSARs and the predictions are based on a trend analysis or read-across from 8-10 category members. In all cases categories are generated on the basis of structural similarity, presence of the functional groups and lack of specific alerts for reproductive toxicity according DART scheme. Because QSAR Toolbox only has a limited number of profilers which are specific for reproductive and developmental toxicity endpoints, the Toolbox category definition for these endpoints have to rely on similarities in the physico-chemical and bioavailability data, shared structural features and similar reactivity patterns. As a consequence Toolbox categorisation for high tier endpoints can be consider as a preliminary step to find close analogues while the prediction shall be based on sound read-across hypothesis and supported by high quality experimental data. The categorisation and subcategorization steps taken in your predictions for reproductive and developmental toxicity provide first steps for building a broad category definition.

However there is no relevant experimental data from the closest analogues. In addition, in the categories proposed there are quite significant structural differences and high variation in bioavailability and toxic properties among category members (e.g. Log Kow between 0.99 and 4.47 and NOAELs between 100 and 1000).

To conclude, due to the lack of relevant data from structurally close analogues these QSAR Toolbox predictions cannot be accepted as standalone evidence to cover information requirements. ECHA considers that there is not a reliable basis for predicting the properties of the registered substance "from data for reference substance(s) within the group by interpolation to other substances in the group", as required by Annex XI, 1.5. In consequence, the predictions are not adequate for the purpose of classification and labelling and/or risk assessment as required by Annex XI, Section 1.3. Hence, the predictions are rejected.

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 421/422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with rats.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

ECHA notes that in your comments on the draft decision, you have not provided further experimental information to support the proposed read-across adaptation.

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

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

Notes for your considerations

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

You should also carefully consider the order of testing of the requested screening (OECD TG 421/422) and the developmental toxicity studies (OECD TG 414) to ensure that unnecessary animal testing is avoided, paying particular attention to the endpoint specific guidance[3] Section R.7.6.2.3.2., pages 484 to 485 of version 6.0 – July 2017.

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

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

In the technical dossier you have provided a study record for a pre-natal developmental toxicity study (Ishiguro et al., 1993). You have also provided a QSAR Toolbox prediction for this endpoint.

However, the study by Ishiguro et al. does not provide the information required by Annex IX, Section 8.7.2., because it has been given a reliability of 4. Hence, it does not meet the quality criteria of an acceptable study. Furthermore, the submitted study has been performed with the analogue substance benzyl acetate (EC no 205-399-7). As explained above in section "*Grouping of substances and read-across approach*", your adaptation of the information requirement is rejected.

You have furthermore sought to adapt this information requirement by providing the following waiver: "*In accordance with Annex VIII section 8.7.1 column 2 adaptation this study does not need to be conducted if a two-generation reproductive toxicity study is available. A developmental reproductive toxicity [Q]SAR on the structural similar analogues as defined within within the OECD [Q]SAR toolbox based on DART scheme v.1.0., Organic functional groups, Lipinski Rule OASIS, Structural similarity. Chemical elements, Test guideline, Test type, Test organisims (species), Route of administration, Reliability and Substance type. See section 7.8.1 of IUCLID. Read across to this substance is justified based on similarity in structure and biological activity.*"

However, a pre-natal developmental toxicity study is a standard information requirement for Annex IX under which your substance is registered, and cannot be waived based on the Annex VIII adaptation cited in your waiver. Furthermore, as further explained above in Section 4, the information requirements cannot be fulfilled by the QSAR predictions for toxicity to reproduction. Therefore, your adaptation of the information requirement is rejected.

ECHA notes that in your comments on the draft decision you have not provided further experimental data or other relevant information to support the read-across, which you have proposed.

[3] ECHA's Guidance document: https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf

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 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

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

Notes for your consideration

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

Deadline to submit the requested information

In the draft decision communicated to you the time indicated to provide the requested information was 30 months from the date of adoption of the decision. This period of time took into account the fact that the draft decision also requested a *Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats.* As this study is not addressed in the present decision, ECHA considers that a reasonable time period for providing the required information in the form of an updated registration is 18 months from the date of the adoption of the decision. The decision was therefore modified accordingly.

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 8 June 2017.

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

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

ECHA took into account your comments and amended the requests and the deadline.

Based on your comments on the draft decision, ECHA amended the draft decision by removing the following request: *Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats.* This was due to a re-interpretation by you of the results of the sub-chronic toxicity study. In the current dossier, you set the NOAEL at 150 mg/kg. However, in your comments you stated that "the study conducted and provided in the registration dossier as equivalent to an OECD TG 408 did aim and did achieve inducing some toxicity as shown by increased stomach weights seen in 50 and 150 mg/kg/day females at 2 weeks. Organ weights changes in treated males at week 6 and at 13 weeks were observed in the 150 mg/kg/day males." You also observed that "the clinical signs in the OECD 408 study do give clear indications that toxicity which may not have reached statistical significance, is however proof of changes occurring in males and females."

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

ECHA received a proposal for amendment and did not modify the draft decision.

ECHA invited you to comment on the proposed amendment.

ECHA referred the draft decision to the Member State Committee.

You did not provide any comments on the proposed amendment(s).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-60 written procedure 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 requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.