EUROPEAN CHEMICALS AGENCY

Helsinki, 11 March 2020

Addressees
Registrants of [redacted] listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
13 February 2019

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: 2,2,2-trichloro-1-phenylethyl acetate
EC number: 201-972-0
CAS number: 90-17-5

Decision number: [Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/D)]

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by ***19 December 2022.***

A. Requirements applicable to all the Registrants subject to Annex VII of REACH

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method EU B.13/14. / OECD TG 471) with the Substance;

2. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method EU C.2./OECD TG 202) with the Substance;

3. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method EU C.3./OECD TG 201) with the Substance

B. Requirements applicable to all the Registrants subject to Annex VIII of REACH

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 Substance;

2. Only if both studies under sections A.1 and B.1 have negative results; In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or OECD TG 490) with the Substance;

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

4. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method OECD TG 203) with the Substance

C. Requirements applicable to all the Registrants subject to Annex IX of REACH

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method

OECD TG 408) in rats with the Substance;

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

3. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method EU C.20./OECD TG 211) with the Substance;

4. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method OECD TG 210) with the Substance

Conditions to comply with the requests

Each addressee of this decision is bound by the requests for information corresponding to the REACH Annexes applicable to their own registered tonnage of the Substance at the time of evaluation of the jointly submitted dossier. To identify your legal obligations, please refer to the following:

- you have to comply with the requirements of Annex VII of REACH, if you have registered a substance at 1-10 tonnes per year (tpa) or at a higher tonnage band, or as a transported isolated intermediate in quantity above 1000 tpa;
- you have to comply with the requirements of Annexes VII and VIII of REACH, if you have registered a substance at 10-100 tpa or at a higher tonnage band;
- you have to comply with the requirements of Annexes VII, VIII and IX of REACH, if you have registered a substance at 100-1000 tpa or a higher tonnage band.

The Appendix on general considerations addresses common arguments that are applicable throughout the present decision while the other Appendices state further the reasons for the requests for information to fulfil the requirements set out in the respective Annexes of REACH.

The testing material used to perform the required studies shall be selected and reported in accordance with the specifications prescribed in Appendix Observations and technical guidance.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information. The timeline has been set to allow for sequential testing.

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.

Approved[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

EUROPEAN CHEMICALS AGENCY

Appendix on general considerations

Adaptations according to Annex XI

Your registration dossier contains adaptation arguments for the information requirements addressed in this decision (requests A.1 – C.4) in the form of weight-of-evidence approach according to Annex XI, Section 1.2., and predictions generated with QSAR models according to Annex XI, Section 1.3. A list of references to ECHA Guidance documents containing further information on these adaptations are listed in Appendix E of this decision.

For each relevant endpoint, ECHA has assessed your adaptation arguments in line with the conditions specified in Annex XI of the REACH Regulation:

(i) For the use of adaptations using Weight of Evidence (WoE) according to Annex XI, Section 1.2., it should be demonstrated that there is sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property with respect to the information requirement in question while the information from each single source alone is regarded insufficient to support this notion.

A weight of evidence adaptation shall include an assessment of the relative values/weights of different pieces of the available information which is defined by e.g. the reliability of the data, consistency of results/data, nature and severity of effects, and relevance of the information for the given regulatory endpoint. Subsequently, the lines of evidence should be integrated considering their relative values or weights in order to draw a conclusion (ECHA Guidance R.4).

Adequate and reliable documentation shall be provided to describe your WoE approach, the assessment of relative weights of individual piece of information and the subsequent conclusions drawn.

Whenever sources of information derived from analogue substances are used as part of a WoE, the characterisation of the analogue substance(s) identified needs to be as detailed as possible, the results of the studies have adequate and reliable coverage of the key parameters and a reasoning needs to be provided to establish why information from analogue substance(s) can reliably be read-across.

(ii) For the use of QSAR models under Annex XI, Section 1.3., the following cumulative conditions shall be necessarily met: results are derived from a (Q)SAR model whose scientific validity has been established; the substance falls within the applicability domain of the model; results are adequate for the purpose of classification and labelling and/or risk assessment; adequate and reliable documentation of the applied method is provided.

Appendix A: Reasons for the requests to comply with Annex VII of REACH

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 1 to 10 tonnes or more per year must contain, as a minimum, the information specified in Annex VII to the REACH Regulation.

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.);

An *In vitro* gene mutation study in bacteria is a standard information requirement in Annex VII to REACH.

You have adapted this information requirement by using a weight of evidence (WoE) approach under Annex XI, Section 1.2., by providing two endpoint study records with analogue substances:

with benzyl acetate / EC: 205-399-7 / CAS: 140-11-4

(i) *In vitro* bacterial gene mutation test (equivalent to OECD TG 471, no GLP, publication)

with methyl benzoate/ EC: 202-259-7 / CAS: 93-58-3

(ii) *In vitro* bacterial gene mutation test (read-across and WoE, equivalent to OECD TG 471, no GLP, publication)

The conditions for adapting the standard information requirement under Annex XI, Section 1.2. are explained in the Appendix on general considerations above.

We have assessed the provided information and identified the following issues:

With regard to the information from analogue substances, used as part of WoE, you have not provided:

- detailed information on the identity of the source substance(s) in particular the composition of the test material(s); and
- any reasoning establishing why information from analogue substance(s) can reliably contribute to the WoE adaptation to conclude on the presence or absence of the particular dangerous property of the Substance.

In addition, ECHA observes the following: First, to fulfil the information requirements of OECD TG 471 (1997), the test should be performed with 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101).
However, the studies you have provided are performed with four of the required five strains. None of the studies used the required fifth strain, *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101). Therefore, the studies are not providing adequate and reliable coverage of the key parameters.

Second, as explained above under General considerations, the reliability of the data is an important parameter of the WoE approach. The provided studies are not GLP compliant. The uncertainty of the conditions under which the studies have been conducted affects the assessment of the reliability of this information. You have not explained how this limitation affects the use of this information as part of the WoE approach.

You have in particular not provided documentation to your WoE approach which would include an assessment of relative weights of the individual pieces of information and the subsequent conclusions drawn.

In conclusion, it is not apparent how the relative value and weight of the above pieces of the available information alone or considered together would be sufficient to allow conclusions that the Substance has or has not the dangerous property as investigated in an *in vitro* gene mutation study in bacteria on the Substance.

Therefore, your adaptation according to Annex XI, Section 1.2. is rejected and the information requirement is not fulfilled.

In your comments on the draft decision, you acknowledge that the information requirement is not fulfilled for this endpoint and you agree to perform the requested study.

2. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)

Short-term toxicity testing on aquatic invertebrates is a standard information requirement in Annex VII to REACH.

You have provided a key study "Short term toxicity of test chemical on daphnia magna" (2018).

According to Article 13(4) of REACH, ecotoxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP). According to Article 141(2), Article 13 applies from entry into application of the REACH Regulation on 1 June 2008.

The study you provided was conducted according to OECD TG 202 but it was not performed in compliance with GLP.

In your comments to the draft decision you confirmed that the reported key study was not performed in a GLP accredited laboratory.

In your comments to the draft decision you also claimed that "*Further classification of our target chemical was supported using weight of evidence approach with read-across analogues were used which is based on functional similarity along with the mechanistic approach compared from QSAR toolbox v3.4.*". In your comments to the draft decision you have referred to:

(i) A study on the Substance (CAS No. 90-17-5) according to OECD TG 202,
(ii) A study on the similar substance benzyl butyrate (CAS No. 103-37-7), and
(iii) A study on the similar substance 2-phenylethyl butyrate (CAS No. 103-52-6).

Finally, in your comments to the draft decision you claim that the data from all studies reported in your comments and the ready biodegradability of the Substance indicate that the Substance is nontoxic and not classified as per CLP classification criteria. On that basis you ask ECHA to remove the request of the study from the draft decision.

Use of information from similar substances in WoE adaptations

In your comments to the draft decision you identified information on the similar substances benzyl butyrate (CAS No. 103-37-7) and 2-phenylethyl butyrate (CAS No. 103-52-6) and considered this information in your adaptation.

Justification for the relevance of information

As indicated in the Appendix on General considerations, and in accordance with the ECHA Guidance R.4, Section R.4.3.2.2., a scientific justification needs to establish why the toxicological or ecotoxicological properties of the Substance can be determined from information on the similar substances. It should also explain why the differences between these substances should not influence the toxicological/ ecotoxicological properties of the Substance or should do so in a regular predictable pattern.

You have attached a document to your comments to the draft decision and intended to justify the use of information obtained on the similar substances CAS 103-37-7 and CAS 103-52-6 in your WoE adaptation for this endpoint. This document presents a set of physico-chemical properties and alerts obtained from the QSAR Toolbox v3.4 for the Substance and for each of these similar substances. On the basis of this information you derive conclusions on the structural similarities, similarities in physico-chemical properties and similarities in the alert profiles between the Substance and the above similar substance. You conclude that "*Based on functional similarity, reactivity, half-life property, metabolism, physical–chemical properties and aquatic acute toxicity by verhaar, OASIS and ECOSAR, benzyl butyrate (103-37-7), 2-phenylethyl butyrate (103-52-6), benzyl propionate (122-63-4) and 2-bromovinyl)benzene (103-64-0) were identified as read-across materials with sufficient data for toxicological evaluation.*".

Provided that the applicability domain is appropriate, the results from using QSAR models may be used in a weight of evidence analysis where such data are considered alongside other relevant data. Considering the complexity and amount of information needed from various function and parameters to evaluate endpoints such as short-term toxicity to aquatic invertebrates QSAR predictions alone do not establish that structurally similar substances have similar properties for these endpoints. You have not provided robust scientific information, including relevant and reliable studies of comparable design and duration, establishing why the ecotoxicological properties of the Substance can be determined from information on the similar substances benzyl butyrate (CAS No. 103-37-7) and 2-phenylethyl butyrate (CAS No. 103-52-6). Therefore the information from studies (ii) and (iii) are considered as not relevant for this WoE adaptation.

Reliability of information on similar substances

Under Article 10(a)(vii) of the REACH Regulation, a technical dossier must include "*robust study summaries of the information derived from the application of Annexes VII to XI, if required under Annex I*". Annex I, Section 1.1.4/3.1.5 of REACH states that robust study summaries are "*required of all key data used in the hazard assessment*".

In the document attached to your comments to the draft decision you have identified studies conducted with the similar substances benzyl butyrate (CAS No. 103-37-7) and 2-phenylethyl butyrate (CAS No. 103-52-6) that you intend to use as sources of information in your weight of evidence approach and you have provided high-level narratives presenting the studies with the above similar substances.

You have not provided robust study summaries for any for these source studies. In particular you have not provided detailed information on the methods, results and conclusions of these studies allowing for an independent assessment of the studies. In the absence of such

information, we cannot assess the reliability of the information from these studies.

Requirement for documentation of the WoE adaptation

With reference to the conditions for adaptations under Annex XI, Section 1.2, which ECHA further explained in the Appendix on general considerations above, it is not apparent how the relative value and weight of the above pieces of the available information alone or considered together would be sufficient to allow conclusions that the Substance has or has not the dangerous property investigated in a short-term toxicity study on aquatic invertebrates.

You have in particular not provided documentation to your WoE approach which would include an assessment of the relative weights of the individual pieces of information and the subsequent conclusions drawn. In each of the endpoint-specific sections of your comments to the draft decision you described the sources of information that you considered in your WoE adaptation and concluded that with this information you consider that you have been able to fulfil the different information requirements.

Whilst these summaries can be regarded as integrated summaries of the data sets, you have not communicated and documented in a robust and transparent manner your considerations on the relevance, reliability of the individual sources of information. No critical assessment of their relative weight and of the overall adequacy of the data set in the context of these WoE is included in the documentation of your adaptations.

Use of classification as an adaptation

Non-classification under the CLP regulation based on the information in your comments to the draft decision is not a valid waiver in Annex VII, Section 9.1, column 2 or under the General rules for adaptation under Annex XI.

Conclusion

Therefore, your adaptation according to Annex XI, Section 1.2. is rejected and the information requirement is not fulfilled.

3. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

Growth inhibition study aquatic plants is a standard information requirement in Annex VII to REACH.

You have provided a key study "Effect of test chemical on the Fresh water algae" (2018).

According to Article 13(4) of REACH, ecotoxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP). According to Article 141(2), Article 13 applies from entry into application of the REACH Regulation on 1 June 2008.

The study you provided was conducted according to OECD TG 201 but it was not performed in compliance with GLP.

In your comments to the draft decision you confirmed that the reported key study was not performed in a GLP accredited laboratory.

In your comments to the draft decision you also claimed that "*Further classification of our target chemical was supported using weight of evidence approach with read-across analogues were used which is based on functional similarity along with the mechanistic approach compared from QSAR toolbox v3.4.*". In your comments to the draft decision you have referred to:

(i) A study on the Substance (CAS No. 90-17-5) according to OECD TG 201,
(ii) A study on the similar substance benzyl propionate (CAS No. 122-63-4), and
(iii)A study on the similar substance 2-bromovinylbenzene (CAS No. 103-64-0).

Finally, in your comments to the draft decision you claim that the data from all studies reported in your comments and the ready biodegradability of the Substance indicate that the Substance is nontoxic and not classified as per CLP classification criteria. On that basis you ask ECHA to remove the request of the study from the draft decision.

Use of information from similar substances in WoE adaptations

In your comments to the draft decision you identified information on the similar substances benzyl propionate (CAS No. 122-63-4) and 2-bromovinylbenzene (CAS No. 103-64-0) and considered this information in your adaptation.

Justification for the relevance of information

As indicated in the Appendix on General considerations, and in accordance with the ECHA Guidance R.4, Section R.4.3.2.2., a scientific justification needs to establish why the toxicological or ecotoxicological properties of the Substance can be determined from information on the similar substances. It should also explain why the differences between these substances should not influence the toxicological/ ecotoxicological properties of the Substance or should do so in a regular predictable pattern.

You have attached a document to your comments to the draft decision and intended to justify the use of information obtained on the similar substances CAS 122-63-4 and CAS 103-64-0 in your WoE adaptation for this endpoint. This document presents a set of physico-chemical properties and alerts obtained from the QSAR Toolbox v3.4 for the Substance and for each of these similar substances. On the basis of this information you derive conclusions on the structural similarities, similarities in physico-chemical properties and similarities in the alert profiles between the Substance and the above similar substance. You conclude that "*Based on functional similarity, reactivity, half-life property, metabolism, physical–chemical properties and aquatic acute toxicity by verhaar, OASIS and ECOSAR, benzyl butyrate (103-37-7), 2-phenylethyl butyrate (103-52-6), benzyl propionate (122-63-4) and 2-bromovinyl)benzene (103-64-0) were identified as read-across materials with sufficient data for toxicological evaluation.*".

Provided that the applicability domain is appropriate, the results from using QSAR models may be used in a weight of evidence analysis where such data are considered alongside other relevant data. Considering the complexity and amount of information needed from various function and parameters to evaluate endpoints such as growth inhibition on aquatic plants QSAR predictions alone do not establish that structurally similar substances have similar properties for these endpoints. You have not provided robust scientific information, including relevant and reliable studies of comparable design and duration, establishing why the ecotoxicological properties of the Substance can be determined from information on the similar substances benzyl propionate (CAS No. 122-63-4) and 2-bromovinylbenzene (CAS No. 103-64-0). Therefore the information from studies (ii) and (iii) are considered as not relevant

for this WoE adaptation.

Reliability of information on similar substances

Under Article 10(a)(vii) of the REACH Regulation, a technical dossier must include "*robust study summaries of the information derived from the application of Annexes VII to XI, if required under Annex I*". Annex I, Section 1.1.4/3.1.5 of REACH states that robust study summaries are "*required of all key data used in the hazard assessment*".

In the document attached to your comments to the draft decision you have identified studies conducted with the similar substances benzyl propionate (CAS No. 122-63-4) and 2-bromovinylbenzene (CAS No. 103-64-0) that you intend to use as sources of information in your weight of evidence approach and you have provided high-level narratives presenting the studies with the above similar substances.

You have not provided robust study summaries for any for these source studies. In particular you have not provided detailed information on the methods, results and conclusions of these studies allowing for an independent assessment of the studies. In the absence of such information, we cannot assess the reliability of the information from these studies.

Requirement for documentation of the WoE adaptation

With reference to the conditions for adaptations under Annex XI, Section 1.2, which ECHA further explained in the Appendix on general considerations above, it is not apparent how the relative value and weight of the above pieces of the available information alone or considered together would be sufficient to allow conclusions that the Substance has or has not the dangerous property investigated in a growth inhibition study on aquatic plants.

You have in particular not provided documentation to your WoE approach which would include an assessment of the relative weights of the individual pieces of information and the subsequent conclusions drawn. In each of the endpoint-specific sections of your comments to the draft decision you described the sources of information that you considered in your WoE adaptation and concluded that with this information you consider that you have been able to fulfil the different information requirements.

Whilst these summaries can be regarded as integrated summaries of the data sets, you have not communicated and documented in a robust and transparent manner your considerations on the relevance, reliability of the individual sources of information. No critical assessment of their relative weight and of the overall adequacy of the data set in the context of these WoE is included in the documentation of your adaptations.

Use of classification as an adaptation

Non-classification under the CLP regulation based on the information in your comments to the draft decision is not a valid waiver in Annex VII, Section 9.1, column 2 or under the General rules for adaptation under Annex XI.

Conclusion

Therefore, your adaptation according to Annex XI, Section 1.2. is rejected and the information requirement is not fulfilled.

Appendix B: Reasons for the requests to comply with Annex VIII of REACH

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 10 to 100 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII and VIII to the REACH Regulation.

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 in Annex VIII to REACH.

You have adapted this information requirement by using a weight of evidence (WoE) approach under Annex XI, Section 1.2. by providing two endpoint study records with analogue substance benzyl acetate / EC: 205-399-7 / CAS: 140-11-4:

(i) *In vitro* cytogenicity test (equivalent to OECD TG 473, GLP not specified; 2015), performed in CHO-W-B1 (cloned Chinese hamster ovary) cell line with and without metabolic activation.

(ii) *In vitro* cytogenicity test (equivalent to OECD TG 473, GLP not specified; 2015), performed in CHL/IU (cloned Chinese hamster lung fibroblast) cell line with and without metabolic activation.

We have assessed the provided information and identified the following issues:

With regard to the information from analogue substances, used as part of WoE, you have not provided:

- detailed information on the identity of the source substance(s) in particular the composition of the test material(s);
- any reasoning establishing why information from analogue substance(s) can reliably contribute to the WoE adaptation to conclude on the presence or absence of the particular dangerous property of the Substance.

In the absence of this information ECHA cannot contribute any weight to this information in its assessment of the compliance of your adaptation based on WoE.

In addition, ECHA observes the following: First, to fulfil the information requirement of OECD TG 473 or OECD TG 487, the following key paramaters have to be covered:

a) The maximum concentration tested must induce 55+5% of cytotoxicity compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test concentration must correspond to 10 mM, 2 mg/mL or 2 µl/mL, whichever is the lowest.
b) At least 300 well-spread metaphases must be scored per concentration
c) The number of cells with structural chromosomal aberrations (breaks excluding gaps, exchanges) must be reported
d) a negative control with a response inside the historical control range of the laboratory.

The reported data for the studies (i) and (ii) did not include:

a) a maximum tested concentration of 10 mM, 2 mg/mL or 2 µl/mL, or that induced 55+5% of cytotoxicity compared to the negative control, or the precipitation of the tested substance.

b) the scoring of at least 300 metaphases per concentration. In the studies above, only 100 metaphases per concentration were scored.
c) The number of cells with structural chromosomal aberrations (breaks excluding gaps, exchanges) are not reported for study (i)
d) a negative control with a response inside the historical control range of the laboratory.

In your comments to the draft decision you tried to address some of the pointed out deficiencies, in particular, the maximum tested concentration by saying that *"the test chemical shows a limiting cytotoxicity, even at the concentration of 2.4 mg/ml NADP, and 4.5 mg/ml isocitric acid in serum-free medium, thus exceeding even the corresponding concentrations of 2 mg/ml, as pointed out ECHA".*

ECHA notes, that the concentrations you are referring to are not the tested concentrations of the analogue substance but the concentrations of the co-factors used in the metabolic activation system.

Further more, as explained above under General considerations, the reliability of the data is an important parameter of the WoE approach. The provided studies are not GLP compliant. The uncertainty of the conditions under which the studies have been conducted affects the assessment of the reliability of this information. You have not explained how this limitation affects the use of this information as part of the WoE approach.

You have further not provided documentation to your WoE approach which would include an assessment of relative weights of the individual pieces of information and the subsequent conclusions drawn.

In your comments to the draft decision you claim that the data for this information requirement is *"supported by strong functionally similar read-across analogue benzyl acetate (CAS: 140-11-4; EC: 205-399-7) from the research articles of Galloway et al. (Environmental and Molecular Mutagenesis, 1987) and Matsuoka et al. (Mutation Research, 1996)".* You did not provide any experimental data with the analogue substance.

Further, you have attached a document to your comments to the draft decision intended to justify the use of information obtained on the similar substances, including CAS: 104-55-2, CAS: 101-41-7, CAS:532-32-1 in your WoE adaptation for this endpoint.

ECHA has assessed the new information and has identified the following issues:

Use of information from similar substances in WoE adaptations

Justification for the relevance of information

As indicated in the Appendix on General considerations, and in accordance with the ECHA Guidance R.4, Section R.4.3.2.2., a scientific justification needs to establish why the toxicological or ecotoxicological properties of the Substance can be determined from information on the similar substances. It should also explain why the differences between these substances should not influence the toxicological/ ecotoxicological properties of the Substance or should do so in a regular predictable pattern.

You have attached a document to your comments to the draft decision and intended to justify the use of information obtained on the similar substances CAS: 104-55-2, CAS: 101-41-7, CAS:532-32-1 in your WoE adaptation for this endpoint. This document presents a set of

physico-chemical properties and alerts obtained from the QSAR Toolbox v3.4 for the Substance and for each of these similar substances. On the basis of this information you derive conclusions on the structural similarities, similarities in physico-chemical properties and similarities in the alert profiles between the Substance and the above similar substance. You conclude that "*Based on functional similarity, reactivity, half-life property, metabolism, physical–chemical properties, and databases such as Protein binding by OECD, Carcinogenicity (genotox and nongenotox) alerts by ISS, in vitro mutagenicity (Ames test) alerts by ISS, Repeated dose (HESS), Estrogen Receptor Binding and DART scheme v.1.0 the chemicals, methyl phenyl acetate (CAS No. 101-41-7), Cinnamaldehyde (104-55-2) and benzoic acid, sodium salt (1:1) (532-32-1) were identified as read-across materials with sufficient data for toxicological evaluation*".

Provided that the applicability domain is appropriate, the results from using QSAR models may be used in a weight of evidence analysis where such data are considered alongside other relevant data. Considering the complexity and amount of information needed from various function and parameters to evaluate endpoints such as genotoxicity, QSAR predictions alone do not establish that structurally similar substances have similar properties for these endpoints. You have not provided robust scientific information, including relevant and reliable studies of comparable design and duration, establishing why the ecotoxicological properties of the Substance can be determined from information on the similar substances methyl phenyl acetate (CAS No. 101-41-7), Cinnamaldehyde (104-55-2) and benzoic acid, sodium salt (1:1) (532-32-1). Therefore the information provided is considered as not relevant for this WoE adaptation.

Reliability of information on similar substances

Under Article 10(a)(vii) of the REACH Regulation, a technical dossier must include "*robust study summaries of the information derived from the application of Annexes VII to XI, if required under Annex I*". Annex I, Section 1.1.4/3.1.5 of REACH states that robust study summaries are "*required of all key data used in the hazard assessment*".

ECHA notes that in the document attached to your comments to the draft decision you have not provided a study record with the analogue substance benzyl acetate (*CAS: 140-11-4; EC: 205-399-7)*. However, ECHA points out that a robust study summary, including detailed information on the methods, results and conclusions of the source studies allowing for an independent assessment of the studies must be provided. In the absence of such information, we cannot assess the reliability of the information from these studies.

Requirement for documentation of the WoE adaptation

With reference to the conditions for adaptations under Annex XI, Section 1.2, which ECHA further explained in the Appendix on general considerations above, it is not apparent how the relative value and weight of the above pieces of the available information alone or considered together would be sufficient to allow conclusions that the Substance has or has not the dangerous property investigated in a growth inhibition study on aquatic plants.

You have in particular not provided documentation to your WoE approach which would include an assessment of the relative weights of the individual pieces of information and the subsequent conclusions drawn. In each of the endpoint-specific sections of your comments to the draft decision you described the sources of information that you considered in your WoE adaptation and concluded that with this information you consider that you have been able to fulfil the different information requirements.

Whilst these summaries can be regarded as integrated summaries of the data sets, you have not communicated and documented in a robust and transparent manner your considerations on the relevance, reliability of the individual sources of information. No critical assessment of their relative weight and of the overall adequacy of the data set in the context of these WoE is included in the documentation of your adaptations.
Finally, in your comments you refer to a test performed according to OECD TG 476.

A study according to OECD TG 476 is a different endpoint (i.e. Annex VIII, Section 8.4.3.), and therefore it cannot be used to fulfil the information requirements for this endpoint.

Conclusion

In conclusion, it is not apparent how the relative value and weight of the above pieces of the available information alone or considered together would be sufficient to allow conclusions that the Substance has or has not the dangerous property as investigated in an *In vitro* cytogenicity study in mammalian cells or an *In vitro* micronucleus study on the Substance.

Therefore, your adaptation according to Annex XI, Section 1.2. is rejected and the information requirement is not fulfilled.

Based on the above, the information you provided do not fulfil the information requirement.

To fulfil the information requirement for the Substance, both *In vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) and *in vitro* micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) are considered suitable.

2. Only if both studies under sections A.1 and B.1 have negative results, In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or OECD TG 490).

An *in vitro* gene mutation study in mammalian cells is a standard information requirement in Annex VIII to REACH in case of a negative result in the Ames test and the *in vitro* cytogenicity test.

ECHA already gave its reasons for the requests for information on an *in vitro* gene mutation study in bacteria and on an *in vitro* cytogenicity study in mammalian cells (ECHA rejects the adaptations based on data on analogue substances, as explained in sections A.1. and B.1. above).

The result of the requests for information A.1. and B.1. will determine whether the present requirement for an *in vitro* mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3 is triggered.

ECHA further considers that the information in your registration dossier does not meet the standard required under REACH. You have provided the following study in your dossier, performed with the Substance:

(i) *In vitro* gene mutation study in mammalian cells with and without metabolic activation (according to OECD TG 476, no GLP compliant, 2015).

However, according to Article 13(4) of REACH, toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP). According to Article 141(2), Article 13 applies from entry into application of the REACH Regulation on 1 June 2008.

The study you provided is not performed in compliance with GLP and can therefore not meet the information requirement under REACH.

In your comments to the draft decision you indicated that the provided study is conducted *"as per the OECD 476 guideline taking the GLP principles into consideration at Lund University under the supervision of expert researchers which supports the non-mutagenic nature of the target chemical"*.

From your comment we understand that the study was not conducted according to GLP principles. We point out that *"taking the GLP principles into consideration"* does not fulfil the requirement that a study must be performed according to the OECD GLP principles.**Error! Bookmark not defined.**

Consequently, you are required to provide information for this endpoint, if the *in vitro* gene mutation study in bacteria and the *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study provides a negative result.

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

A Screening for reproductive/developmental toxicity study (OECD TG 421 or 422) is a standard information requirement under Annex VIII to REACH, if there is no evidence from analogue substances, QSAR or *in vitro* methods that the Substance may be a developmental toxicant. There is no information available in your dossier indicating that your Substance may be a developmental toxicant.

You have provided the following key studies with the Substance in your dossier:

(i) Short-term (28-day) repeated dose toxicity study in rats, via oral-gavage (key study, according to OECD TG 407, GLP compliant, 2014);
(ii) Short-term (28-day) repeated dose toxicity study in rat, dermal route (key study, according to OECD TG 410, GLP compliant, 2013).

In addition, you have provided the following information on analogue substances:

(iii) Pre-natal developmental toxicity study in mice with 3-phenylacrylaldehyde / EC: 203-213-9 / CAS: 104-55-2 (supporting study, equivalent to OECD TG 414, GLP not specified; Hardin B.D. et al., 1987);

(iv) Screening for reproductive / developmental toxicity study in rats with methyl phenylacetate / EC: 202-940-9 / CAS: 101-41-7 (supporting study, according to OECD TG 422, GLP compliant; 2016).

We have assessed this information and identified the following issue(s):

To be considered compliant and to generate information concerning the effects of the Substance on male and female reproductive performance as well as specific target organ toxicity, the study has to meet the requirements of OECD TG 421/422, in particular:

- Dosing of the Substance for a minimum of four weeks for males and approx. 63 days for females to cover premating, conception, pregnancy and at least 13 days of lactation
- Examination of key parameters for toxicity such as clinical signs/body weight/body weight changes/food consumption/thyroid hormone assessment (P0 and F1)
- Monitoring of oestrus cycles

However, the studies under points (i) and (ii) above do not fulfil the above criteria, because the 28-day short-term study:

- does not have the required exposure duration, i.e. it does not cover the relevant life stages (two weeks of premating and pregnancy and at least 13 days of lactation);
- does not cover key parameters of reproductive performance such as gonadal function, mating behaviour, conception, development of the conceptus and parturition.
- does not monitor the oestrus cycles

Regarding the supporting studies (iii) and (iv), ECHA observes that the information is on analogue substances. However, no explanation is provided how this information would allow conclusions on the properties of the Substance. Hence, ECHA cannot attribute any weight to this information.

In your comments to the draft decision you state that the information you have provided with the Substance and the analogue substances is enough to conclude that the Substance is not a reproductive toxicant.

ECHA reiterates that a short-term (28-day) toxicity study does not fulfill the information requirements for OECD TG 421/422 due to the reasons explained above.

Further, you have attached a document to your comments to the draft decision intended to justify the use of information obtained on the similar substances, including CAS: 104-55-2, CAS: 101-41-7 in your WoE adaptation for this endpoint.

ECHA has assessed the new information and has identified the following issues:

Use of information from similar substances in WoE adaptations

Justification for the relevance of information

As indicated in the Appendix on General considerations, and in accordance with the ECHA Guidance R.4, Section R.4.3.2.2., a scientific justification needs to establish why the toxicological or ecotoxicological properties of the Substance can be determined from information on the similar substances. It should also explain why the differences between these substances should not influence the toxicological/ ecotoxicological properties of the Substance or should do so in a regular predictable pattern.

You have attached a document to your comments to the draft decision and intended to justify the use of information obtained on the similar substances CAS: 104-55-2, CAS: 101-41-7, in your WoE adaptation for this endpoint. This document presents a set of physico-chemical properties and alerts obtained from the QSAR Toolbox v3.4 for the Substance and for each of these similar substances. On the basis of this information you derive conclusions on the structural similarities, similarities in physico-chemical properties and similarities in the alert profiles between the Substance and the above similar substance. You conclude that "*Based on functional similarity, reactivity, half-life property, metabolism, physical–chemical properties, and databases such as Protein binding by OECD, Carcinogenicity (genotox and*

nongenotox) alerts by ISS, in vitro mutagenicity (Ames test) alerts by ISS, Repeated dose (HESS), Estrogen Receptor Binding and DART scheme v.1.0 the chemicals, methyl phenyl acetate (CAS No. 101-41-7), Cinnamaldehyde (104-55-2) and benzoic acid, sodium salt (1:1) (532-32-1) were identified as read-across materials with sufficient data for toxicological evaluation".

Provided that the applicability domain is appropriate, the results from using QSAR models may be used in a weight of evidence analysis where such data are considered alongside other relevant data. Considering the complexity and amount of information needed from various function and parameters to evaluate endpoints such as reproductive toxicity, QSAR predictions alone do not establish that structurally similar substances have similar properties for these endpoints. You have not provided robust scientific information, including relevant and reliable studies of comparable design and duration, establishing why the ecotoxicological properties of the Substance can be determined from information on the similar substances methyl phenyl acetate (CAS No. 101-41-7) and Cinnamaldehyde (104-55-2). Therefore the information provided is considered as not relevant for this WoE adaptation.

Requirement for documentation of the WoE adaptation

With reference to the conditions for adaptations under Annex XI, Section 1.2, which ECHA further explained in the Appendix on general considerations above, it is not apparent how the relative value and weight of the above pieces of the available information alone or considered together would be sufficient to allow conclusions that the Substance has or has not the dangerous property investigated in a growth inhibition study on aquatic plants.

You have in particular not provided documentation to your WoE approach which would include an assessment of the relative weights of the individual pieces of information and the subsequent conclusions drawn. In each of the endpoint-specific sections of your comments to the draft decision you described the sources of information that you considered in your WoE adaptation and concluded that with this information you consider that you have been able to fulfil the different information requirements.

Whilst these summaries can be regarded as integrated summaries of the data sets, you have not communicated and documented in a robust and transparent manner your considerations on the relevance, reliability of the individual sources of information. No critical assessment of their relative weight and of the overall adequacy of the data set in the context of these WoE is included in the documentation of your adaptations.

Conclusion

Therefore, your adaptation according to Annex XI, Section 1.2. is rejected and the information requirement is not fulfilled.

Based on the above, the information you provided do not fulfil the information requirement.

Information on the study design

A study according to the test method OECD TG 421/422 should be performed in rats with oral[2] administration of the Substance.

[2] ECHA Guidance R.7a, Section R.7.6.2.3.2.

4. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

Short-term toxicity testing on fish is a standard information requirement in Annex VIII to REACH.

You have provided a key study "Acute Toxicity Study of 2,2,2-trichloro-1-phenylethyl acetate (CAS No. 90-17-5) on Zebra Fish in a Static System (96 hours))" (2015).

According to Article 13(4) of REACH, ecotoxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP). According to Article 141(2), Article 13 applies from entry into application of the REACH Regulation on 1 June 2008.

The study you provided was conducted according to OECD TG 203 but it was not performed in compliance with GLP.

In your comments to the draft decision you admit that the reported study is "*...as per OECD guideline 203 but not from the GLP lab...*".

In your comments to the draft decision you also claimed that "*The experimental study for the target chemical (2,2,2-trichloro-1-phenylethyl acetate (90-17-5) was supported by another two supporting studies for read across chemicals benzyl propionate (122-63-4) and benzyl butyrate (103-37-7) which supports the classification of target chemical.*" In your comments to the draft decision you have referred to:

(i) A study on the Substance (CAS No. 90-17-5) according to OECD TG 203,
(ii) A study on the similar substance benzyl propionate (CAS No. 122-63-4), and
(iii)A study on the similar substance benzyl butyrate (CAS No. 103-37-7).

Finally, in your comments to the draft decision you claim that the data from all studies reported in your comments and the ready biodegradability of the Substance indicate that the Substance is nontoxic and not classified as per CLP classification criteria. On that basis you ask ECHA to remove the request of the study from the draft decision.

We have assessed this information and identified the following issue(s):

Justification for the relevance of information

As indicated in the Appendix on General considerations, and in accordance with the ECHA Guidance R.4, Section R.4.3.2.2., a scientific justification needs to establish why the toxicological or ecotoxicological properties of the Substance can be determined from information on the similar substances. It should also explain why the differences between these substances should not influence the toxicological/ ecotoxicological properties of the Substance or should do so in a regular predictable pattern.

You have attached a document to your comments to the draft decision and intended to justify the use of information obtained on the similar substances CAS 122-63-4 and CAS 103-37-7 in your WoE adaptation for this endpoint. This document presents a set of physico-chemical properties and alerts obtained from the QSAR Toolbox v3.4 for the Substance and for each of these similar substances. On the basis of this information you derive conclusions on the structural similarities, similarities in physico-chemical properties and similarities in the alert profiles between the Substance and the above similar substance. You conclude that "*Based*

on functional similarity, reactivity, half-life property, metabolism, physical–chemical properties and aquatic acute toxicity by verhaar, OASIS and ECOSAR, benzyl butyrate (103-37-7), 2-phenylethyl butyrate (103-52-6), benzyl propionate (122-63-4) and 2-bromovinyl)benzene (103-64-0) were identified as read-across materials with sufficient data for toxicological evaluation.".

Provided that the applicability domain is appropriate, the results from using QSAR models may be used in a weight of evidence analysis where such data are considered alongside other relevant data. Considering the complexity and amount of information needed from various function and parameters to evaluate endpoints such as short-term toxicity on fish QSAR predictions alone do not establish that structurally similar substances have similar properties for these endpoints. You have not provided robust scientific information, including relevant and reliable studies of comparable design and duration, establishing why the ecotoxicological properties of the Substance can be determined from information on the similar substances benzyl propionate (CAS No. 122-63-4) and benzyl butyrate (CAS No. 103-37-7). Therefore the information from studies (ii) and (iii) are considered as not relevant for this WoE adaptation.

Reliability of information on similar substances

Under Article 10(a)(vii) of the REACH Regulation, a technical dossier must include "*robust study summaries of the information derived from the application of Annexes VII to XI, if required under Annex I*". Annex I, Section 1.1.4/3.1.5 of REACH states that robust study summaries are "*required of all key data used in the hazard assessment*".

In the document attached to your comments to the draft decision you have identified studies conducted with the similar substances benzyl propionate (CAS No. 122-63-4) and benzyl butyrate (CAS No. 103-37-7) that you intend to use as sources of information in your weight of evidence approach and you have provided high-level narratives presenting the studies with the above similar substances.

You have not provided robust study summaries for any for these source studies. In particular you have not provided detailed information on the methods, results and conclusions of these studies allowing for an independent assessment of the studies. In the absence of such information, we cannot assess the reliability of the information from these studies.

Requirement for documentation of the WoE adaptation

With reference to the conditions for adaptations under Annex XI, Section 1.2, which ECHA further explained in the Appendix on general considerations above, it is not apparent how the relative value and weight of the above pieces of the available information alone or considered together would be sufficient to allow conclusions that the Substance has or has not the dangerous property investigated in a short-term toxicity study on fish.

You have in particular not provided documentation to your WoE approach which would include an assessment of the relative weights of the individual pieces of information and the subsequent conclusions drawn. In each of the endpoint-specific sections of your comments to the draft decision you described the sources of information that you considered in your WoE adaptation and concluded that with this information you consider that you have been able to fulfil the different information requirements.

Whilst these summaries can be regarded as integrated summaries of the data sets, you have not communicated and documented in a robust and transparent manner your considerations

on the relevance, reliability of the individual sources of information. No critical assessment of their relative weight and of the overall adequacy of the data set in the context of these WoE is included in the documentation of your adaptations.

Use of classification as an adaptation

Non-classification under the CLP regulation based on the information in your comments to the draft decision is not a valid waiver in Annex VII, Section 9.1, column 2 or under the General rules for adaptation under Annex XI.

Conclusion

Therefore, your adaptation according to Annex XI, Section 1.2. is rejected.

Appendix C: Reasons for the requests to comply with Annex IX of REACH

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII-IX to the REACH Regulation.

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

A Sub-chronic toxicity study (90 day) is a standard information requirement in Annex IX to REACH.

You have provided two key studies for this endpoint with the Substance in your dossier:

(i) Short-term (28-day) repeated dose toxicity study in rats, via oral-gavage (key study, according to OECD TG 407, GLP compliant, 2014).
(ii) Short-term (28-day) repeated dose toxicity study in rat, dermal route (key study, according to OECD TG 410, GLP compliant, 2013).

We have assessed this information and identified the following issue(s):

To be considered compliant and enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL), a study has to meet the requirements of OECD TG 408. The following key parameter(s) of this test guideline include, among others:

- dosing of the Substance daily for a period of 90 days until the scheduled termination of the study,
- At least 10 female and 10 male animals should be used at each dose level (including control group), and
- key parameters measured, for example thyroid hormone.

However, the studies you have provided do not fulfil the above criteria because the 28-day short-term studies

- do not have the required exposure duration of 90 days,
- were conducted with less than 10 animals per sex per test dose group. Thus the statistical power of the information provided is not sufficient because it does not fulfil the criterion of 20 animals (10 males + 10 females) for each test group set in OECD TG 408,
- the thyroid hormone measurements have not been conducted,

In your comments to the draft decision you refer to studies (i) and (ii) as "indicating no safety concern". In addition, you refer to the Annex IX, Section 8.6.2. Column 2, fourth indent and conclude that "*the target chemical fulfills all the requirements*".

Firstly, ECHA reiterates that a short-term (28-day) toxicity study does not fulfill the information requirements for OECD TG 408 due to the reasons explained above.

Secondly, based on your comments, ECHA understands that you propose to adapt this information requirement in accordance with Annex IX, Section 8.6.2. Column 2, fourth indent. ECHA has assessed the possibility for adaptation and identified the following deficiencies:

As provided in Annex IX, Section 8.6.2, Column 2 fourth indent, you may adapt the information requirement, provided the Substance is unreactive, insoluble and not inhalable

and there is no evidence of absorption/of toxicity in a 28-day 'limit test', particularly if it is coupled with limited human exposure.

Based on the information in the registration dossier:

- The water solubility of the Substance is 16.56 mg/L at 25°C which qualifies it as slightly water soluble
- The vapour pressure of the Substance is 0.342 Pa, which qualifies it as inhalable
- The Substance has reported wide-spread professional, workers and consumer uses. In addition the calculated risc charectarisation ratios (RCRs) do not indicate limited human exposure (e.g. for consumers RCR dermal systemic exposure is [redacted] for PROC 8b RCR combined systemic exposure is [redacted] for PROC 11 RCR combined systemic exposure is [redacted]

Based on this information, you have not met the criteria above, as the Substance is water soluble, inhalable and does not have limitet human exposure.

Therefore, the information you provided do not fulfil the information requirement.

Information on the study design

According to the OECD TG 408 rat is the preferred species.

ECHA considers that the oral route is the most appropriate route of administration to investigate repeated dose toxicity, as the Substance is a solid particulate/powder. ECHA acknowledges that there is information indicating likeliness of human exposure by inhalation (PROC 7 and PROC 11). However, the reported concentrations are low (< 1%).

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

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement in Annex IX to REACH.

You have adapted this information requirement by using a weight of evidence (WoE) approach under Annex XI, Section 1.2. by providing study records with analogue substances:

with 3-phenylacrylaldehyde / EC: 203-213-9 / CAS: 104-55-2

(i) Pre-natal developmental toxicity study in mice (WoE, equivalent to OECD TG 414, GLP not specified; Hardin B.D. et al., 1987);

with methyl phenylacetate / EC: 202-940-9 / CAS: 101-41-7

(ii) Screening for reproductive/developmental toxicity study in rats (key study-WoE, according to OECD TG 422, GLP compliant; 2016);

with benzoic acid sodium salt / EC: 208-534-8 / CAS:532-32-1

(iii) Pre-natal developmental toxicity study in rat, oral-feed (WoE, equivalent to OECD TG 414, GLP not specified, assigned reliability 4; 1978).

The conditions for using the weight of evidence approach (Annex XI, section 1.2) are described in Appendix on general considerations above.

We have assessed this information and identified the following issue(s):

With regard to the information from analogue substances, used as part of WoE, you have not provided:

- detailed information on the identity of the source substance(s) in particular the composition of the test material(s);
- any reasoning establishing why information from analogue substance(s) can reliably contribute to the WoE adaptation to conclude on the presence or absence of the particular dangerous property of the Substance.

In the absence of this information ECHA cannot contribute any weight to this information in its assessment of the compliance of your adaptation based on WoE.

In addition, ECHA observes the following: In order to fulfil the information requirements of OECD TG 414, the following key parameter(s) have to be covered:

- highest dose level should aim to induce some developmental and/or maternal toxicity,
- dosing of the Substance from implantation until the day prior to scheduled caesarean section,
- examination of the dams for weight and histopathology of the thyroid gland. thyroid hormone measurements, gravid uterus weight, uterine content,
- examination of the sex ratio, external, skeletal and soft tissue alterations (variations and malformations), number of resorptions and or live foetuses, measurement of anogenital distance in live rodent foetuses.

None of the studies you have reported, provide adequate and reliable coverage of the key parameters. More specifically:

Study (i) does not meet above criteria because:

- The highest dose level in the study did not induce any developmental and/or maternal toxicity and you have not shown that the aim was to induce toxicity;
- the animals were exposed during GD 6-13. The study does not have a required exposure duration because the exposure duration is not from implantation until the day prior to scheduled caesarean section as required in OECD TG 414;
- the weight and histopathology of the thyroid gland, thyroid hormone measurements, gravid uterus weight and uterine content have not been examined in the dams;
- the sex ratio, the external, skeletal and soft tissue alterations (variations and malformations), number of resorptions and or live foetuses, measurement of anogenital distance in live rodent foetuses have not been examined.

Study (ii) does not provide the information required by Annex IX, Section 8.7.2., because the screening study does not cover key parameters, in particular structural malformations and variations, as required in the pre-natal developmental toxicity study.

Study (iii) has been disregarded by you (Klimish score 4). ECHA agrees that the study is not GLP compliant and the documentation provided does not allow to assess its reliability.

ECHA notes that in your comments you have not addressed the above mentioned deficiencies, on the basis of which ECHA rejected the information based on these studies.

In your comments to the draft decision you refer to studies (i), (ii) and (iii) by stating that the information you have provided with the analogue substances is enough to conclude that the Substance is not a developmental toxicant.

Further, you have attached a document to your comments to the draft decision intended to justify the use of information obtained on the similar substances, including CAS: 104-55-2, CAS: 101-41-7 and CAS:532-32-1 in your WoE adaptation for this endpoint.

ECHA has assessed the new information and has identified the following issues:

Use of information from similar substances in WoE adaptations

Justification for the relevance of information

As indicated in the Appendix on General considerations, and in accordance with the ECHA Guidance R.4, Section R.4.3.2.2., a scientific justification needs to establish why the toxicological or ecotoxicological properties of the Substance can be determined from information on the similar substances. It should also explain why the differences between these substances should not influence the toxicological/ ecotoxicological properties of the Substance or should do so in a regular predictable pattern.

You have attached a document to your comments to the draft decision and intended to justify the use of information obtained on the similar substances CAS: 104-55-2, CAS: 101-41-7 and CAS:532-32-1 in your WoE adaptation for this endpoint. This document presents a set of physico-chemical properties and alerts obtained from the QSAR Toolbox v3.4 for the Substance and for each of these similar substances. On the basis of this information you derive conclusions on the structural similarities, similarities in physico-chemical properties and similarities in the alert profiles between the Substance and the above similar substance. You conclude that "*Based on functional similarity, reactivity, half-life property, metabolism, physical–chemical properties, and databases such as Protein binding by OECD, Carcinogenicity (genotox and nongenotox) alerts by ISS, in vitro mutagenicity (Ames test) alerts by ISS, Repeated dose (HESS), Estrogen Receptor Binding and DART scheme v.1.0 the chemicals, methyl phenyl acetate (CAS No. 101-41-7), Cinnamaldehyde (104-55-2) and benzoic acid, sodium salt (1:1) (532-32-1) were identified as read-across materials with sufficient data for toxicological evaluation*".

Provided that the applicability domain is appropriate, the results from using QSAR models may be used in a weight of evidence analysis where such data are considered alongside other relevant data. Considering the complexity and amount of information needed from various function and parameters to evaluate endpoints such as developmental toxicity, QSAR predictions alone do not establish that structurally similar substances have similar properties for these endpoints. You have not provided robust scientific information, including relevant and reliable studies of comparable design and duration, establishing why the ecotoxicological properties of the Substance can be determined from information on the similar substances methyl phenyl acetate (CAS No. 101-41-7), Cinnamaldehyde (104-55-2) and benzoic acid, sodium salt (1:1) (532-32-1). Therefore the information provided is considered as not relevant for this WoE adaptation.

Requirement for documentation of the WoE adaptation

With reference to the conditions for adaptations under Annex XI, Section 1.2, which ECHA further explained in the Appendix on general considerations above, it is not apparent how the

relative value and weight of the above pieces of the available information alone or considered together would be sufficient to allow conclusions that the Substance has or has not the dangerous property investigated in a growth inhibition study on aquatic plants.

You have in particular not provided documentation to your WoE approach which would include an assessment of the relative weights of the individual pieces of information and the subsequent conclusions drawn. In each of the endpoint-specific sections of your comments to the draft decision you described the sources of information that you considered in your WoE adaptation and concluded that with this information you consider that you have been able to fulfil the different information requirements.

Whilst these summaries can be regarded as integrated summaries of the data sets, you have not communicated and documented in a robust and transparent manner your considerations on the relevance, reliability of the individual sources of information. No critical assessment of their relative weight and of the overall adequacy of the data set in the context of these WoE is included in the documentation of your adaptations.

In conclusion, it is not apparent how the relative value and weight of the above pieces of the available information alone or considered together would be sufficient to allow conclusions that the Substance has or has not the dangerous property as investigated in a Pre-natal developmental toxicity study.

You have further not provided documentation to your WoE approach which would include an assessment of relative weights of the individual pieces of information and the subsequent conclusions drawn.

Therefore, your adaptation according to Annex XI, Section 1.2. is rejected and the information requirement is not fulfilled.

Based on the above, the information you provided do not fulfil the information requirement.

Information on the study design

A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species with oral administration of the Substance[3].

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

Long-term toxicity testing on aquatic invertebrates is a standard information requirement in Annex IX to the REACH Regulation.

You have adapted the standard information requirement according to Annex XI, Section 1.3., Qualitative or Quantitative structure-activity relationship ((Q)SAR), by providing a calculation as a key study (ECOSAR v1.11, 2018).

ECHA has evaluated this information under Annex XI, Section 1.3, and the conditions specified in the Appendix on general considerations above (point ii therein).
You have not provided any documentation containing:

[3] ECHA Guidance R.7a, Section R.7.6.2.3.2.

1. An evaluation of the scientific validity (relevance and reliability) of the model used for the prediction,
2. An assessment of the applicability of the model to the Substance and the reliability of the individual model prediction, and
3. An assessment of the adequacy of the prediction for classification and labelling and/or risk assessment.

In the absence of this information, your adaptation does not meet the conditions of Annex XI, Section 1.3. and is therefore rejected. Consequently, the information you provided does not fulfil the information requirement.

In your comments to the draft decision, you now intend to use a weight-of-evidence adaptation to fulfil this information requirement and you have referred to:

(i) An OECD TG 211 study on the "*target chemical*", and
(ii) a new QSAR prediction using the ECOSAR tool that provides different NOEC value than that reported originally in the dossier.

We have assessed this information in your comments and identified the following issue(s):

Use of information from the Substance and QSAR prediction in WoE adaptations

Reliability of information

Under Article 10(a)(vii) of the REACH Regulation, a technical dossier must include "*robust study summaries of the information derived from the application of Annexes VII to XI, if required under Annex I*". Annex I, Section 1.1.4/3.1.5 of REACH states that robust study summaries are "*required of all key data used in the hazard assessment*".

In the document attached to your comments to the draft decision you have identified a study conducted with the "*target chemical*" (no CAS or EC number provided) that you intend to use as one source of information in your weight of evidence approach and you have provided high-level narrative presenting the study with this "*target chemical*".

You have not provided robust study summary for this study. In particular you have not provided detailed information on the test material, methods, results and conclusions of the study allowing for an independent assessment of the study. In the absence of such information, we cannot assess the reliability of the information from this study.

In the document attached to your comments to the draft decision you have also reported a new QSAR prediction (ECOSAR, version not provided) that you intend to use as another source of information in your weight of evidence approach. You also claimed that "*as per the ECHA requirements, we have attached the QMRF report for the predictions attached in these sections to support the results.*"

However, unlike you stated in your comments, you have not attached QMRF and/or QPRF to the comments on the draft decision or on the technical dossier. Therefore, the information content in your comments does not address the concerns identified in the draft decision.

Requirement for documentation of the WoE adaptation

With reference to the conditions for adaptations under Annex XI, Section 1.2, which ECHA further explained in the Appendix on general considerations above, it is not apparent how the

relative value and weight of the above pieces of the available information alone or considered together would be sufficient to allow conclusions that the Substance has or has not the dangerous property investigated in a long-term toxicity study on aquatic invertebrates.

You have in particular not provided documentation to your WoE approach which would include an assessment of the relative weights of the individual pieces of information and the subsequent conclusions drawn. In each of the endpoint-specific sections of your comments to the draft decision you described the sources of information that you considered in your WoE adaptation and concluded that with this information you consider that you have been able to fulfil the different information requirements.

Whilst these summaries can be regarded as integrated summaries of the data sets, you have not communicated and documented in a robust and transparent manner your considerations on the relevance and reliability of the individual sources of information. No critical assessment of their relative weight and of the overall adequacy of the data set in the context of these WoE is included in the documentation of your adaptations.

Conclusion

Therefore, your adaptation according to Annex XI, Section 1.2. is rejected and the information requirement is not fulfilled.

In your comments to the draft decision, you also say that "*long-term toxicity testing on aquatic invertebrates only need to be proposed if the chemical safety assessment according to Annex I indicate the need to investigate further the effects on aquatic organisms. They can be waived based on risk assessment result according to column 2 of Annex IX of REACH regulation.*" You continue that "*Also, classification of the substance is also finalized thus this testing request can be waived.*"

Based on your comment above, ECHA understands that you also intend to adapt this standard information requirement according to Annex IX, Section 9.1.5, Column 2 of REACH.
ECHA has assessed this additional information in your comments and identified the following issue(s):
As specified in Annex IX, Section 9.1., Column 2, a long-term toxicity study on aquatic invertebrates must be performed unless the Chemical Safety Assessment demonstrates that risks towards the aquatic compartment arising from the use of the Substance are controlled (as per Annex I, section 0.1). The justification must be documented in the Chemical Safety Assessment.

In particular, the Chemical Safety Assessment must take into account the following elements to support that long-term toxicity testing is not required:

- all relevant hazard information from your registration dossier,
- the outcome of the exposure assessment in relation to the uses of the Substance,
- the outcome of the PBT/vPvB assessment including information on relevant degradation products and constituents present in concentration at or above 0.1% (w/w).

In your comments on the draft decision, you did not submit any specific justification as to why the risks of the substance are controlled.

As specified in request A2-3, B4, and C3-4 of this decision, the data on aquatic toxicity is not compliant. Hence your dossier currently does not include adequate information to characterize the hazard property of the Substance.

Without this information your Chemical Safety Assessment does not demonstrate that the risks of the Substance are adequately controlled and the Substance is correctly classified for environmental hazards. As a consequence, your adaptation is rejected as it does not meet the specific rules for adaptation of Annex IX,Section 9.1., Column 2.

Based on the above, the information you provided do not fulfil the information requirement.

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

Long-term toxicity testing on fish is a standard information requirement in Annex IX to the REACH Regulation.

You have adapted the standard information requirement according to Annex XI, Section 1.3., Qualitative or Quantitative structure-activity relationship ((Q)SAR), by providing a calculation as a key study (ECOSAR v1.11, 2018).

ECHA has evaluated this information under Annex XI, Section 1.3, and the conditions specified in the Appendix on general considerations above (point ii therein).

You have not provided any documentation containing:

1. An evaluation of the scientific validity (relevance and reliability) of the model used for the prediction,
2. An assessment of the applicability of the model to the Substance and the reliability of the individual model prediction, and
3. An assessment of the adequacy of the prediction for classification and labelling and/or risk assessment.

In the absence of this information, your adaptation does not meet the conditions of Annex XI, Section 1.3. and is therefore rejected. Consequently, the information you provided does not fulfil the information requirement.

In your comments on the draft decision, you agree that long-term toxicity testing on fish is a standard information requirement in Annex IX of REACH and you claim that "*as per the ECHA requirements, we have attached the QMRF report for the predictions attached in these sections to support the results.*"

We note that, unlike you stated in your comments, no QMRF and/or QPRF was attached to the comments on the draft decision or on the technical dossier. Therefore, the information content does not address the concerns identified in the draft decision.

In your comments to the draft decision, you also say that "*long-term toxicity testing on aquatic invertebrates only need to be proposed if the chemical safety assessment according to Annex I indicate the need to investigate further the effects on aquatic organisms. They can be waived based on risk assessment result according to column 2 of Annex IX of REACH regulation.*" You continue that "*Also, classification of the substance is also finalized thus this testing request can be waived.*"

We understand that based on your comment above you intend to adapt this standard information requirement according to Annex IX, Section 9.1.6, Column 2 of REACH.

We have assessed the information in your comments and identified the following issue(s):

As specified in Annex IX, Section 9.1., Column 2, a long-term toxicity study on fish must be performed unless the Chemical Safety Assessment demonstrates that risks towards the aquatic compartment arising from the use of the Substance are controlled (as per Annex I, section 0.1). The justification must be documented in the Chemical Safety Assessment.

In particular, the Chemical Safety Assessment must take into account the following elements to support that long-term toxicity testing is not required:

- all relevant hazard information from your registration dossier,
- the outcome of the exposure assessment in relation to the uses of the Substance,
- the outcome of the PBT/vPvB assessment including information on relevant degradation products and constituents present in concentration at or above 0.1% (w/w).

In your comments on the draft decision, you did not submit any specific justification as to why the risks of the substance are controlled.

As specified in request A2-3, B4 and C3-4 of this decision, the data on aquatic toxicity is not compliant. Hence your dossier currently does not include adequate information to characterize the hazard property of the Substance.

Without this information your Chemical Safety Assessment does not demonstrate that the risks of the Substance are adequately controlled and the Substance is correctly classified for environmental hazards. As a consequence, your adaptation is rejected as it does not meet the specific rules for adaptation of Annex IX,Section 9.1., Column 2.

Therefore, the information requirement is not fulfilled.

Appendix D: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of the REACH Regulation.

The compliance check was initiated on 16 January 2019.

ECHA notified you of the draft decision and invited you to provide comments within 30 days of the notification.

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

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix E: Observations and technical guidance

1. This compliance check decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

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 the Member States.

3. Test guidelines, GLP requirements and reporting

   Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

   Under Article 13(4) of REACH ecotoxicological and toxicological tests and analyses shall be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

   Under Article 10 (a) (vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide: 'How to report robust study summaries[4]'.

4. Testing strategy for aquatic toxicity testing

   Before conducting the aquatic toxicity requested tests (requests A.2, A.3, B.4, C.3, C.4) you should consult the Integrated Testing Strategy described in ECHA Guidance R.7b, Section R.7.8.5 (including Figure R.7.8-4), on the sequence in which the aquatic long-term toxicity tests are to be conducted and the necessity to conduct all the requested studies, in particular the long-term fish toxicity study. Furthermore, REACH Annex VII Section 9.1.1 and Annex VIII Section 9.1.3 describe that you may consider conducting the long-term toxicity testing on daphnia and fish (C.3, C.4) directly instead of short-term testing (A.2, B.4).

   If you decide to omit some of the studies requested in this decision, you must provide full documentation to justify the adaptation.

5. Test material

   Selection of the test material(s)

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

[4] https://echa.europa.eu/practical-guides

While selecting the test material you must take into account the impact of each constituent/impurity is known to have or could have on the test results for the endpoint to be assessed. For example, if a constituent/impurity of the Substance is known to have an impact on (eco)toxicity, the selected test material must contain that constituent/ impurity.

Technical reporting of the test material

The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers" on the ECHA website (https://echa.europa.eu/manuals).

6. List of references of the ECHA Guidance documents[5]

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 in this decision.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[6]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

[5] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[6] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Appendix F: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fufilled
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]