ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 14 December 2018

Addressee: [redacted]

Decision number: CCH-D-2114453633-49-01/F
Substance name: a-methylcinnamaldehyde
EC number: 701-219-0
CAS number: 15174-47-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 13 April 2018
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. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. / OECD TG 471) with the registered substance;**

2. **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;**

3. **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 both studies requested under 1. and 2. have negative results;**

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

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

6. **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 registered substance;**

7. **Robust study summary for "Algae, Growth Inhibition Test According to OECD 201 (March 23, 2006)" (Annex VII, Section 9.1.2. in conjunction with Annex I, Section 3.1.5.);**

8. **Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: Fish, acute toxicity test, OECD TG 203) with the registered substance;**

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

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

11. **Short-term toxicity to terrestrial invertebrates (Annex IX, Section 9.4.1.; test method: Earthworm, acute toxicity tests, EU C.8./OECD TG 207), or,**

    Short-term toxicity to plants (Annex IX, Section 9.4.3. test method: Terrestrial plants, growth test, OECD TG 208), with at least three species tested (with as a minimum one monocotyledonous species and two dicotyledonous species) with the registered substance;

12. **Effects on soil micro-organisms (Annex IX, Section 9.4.2.; test method: Soil microorganisms: nitrogen transformation test, EU C.21/OECD TG 216) and carbon transformation test, EU C.22/OECD TG 217) with the registered substance.**

You have to submit the requested information in an updated registration dossier by ***21 June 2021***. 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.

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[1] by Ofelia Bercaru, Head of Unit, Evaluation E3

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

Appendix 1: Reasons

GENERAL CONSIDERATIONS ON TOXICOLOGICAL AND ECOTOXICOLOGICAL 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 multiple endpoints adaptation arguments in the form of a grouping and read-across approach according to Annex XI, Section 1.5. of the REACH Regulation. ECHA has assessed first the scientific and regulatory validity of your grouping and read-across approach in general before the individual endpoints (sections: 1-12).

Grouping and read-across approach for toxicological and ecotoxicological information

Grouping of substances and read-across approach

You have sought to adapt information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5, for the information requirements:

- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1)
- Sub-chronic toxicity (90-day) study (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.).
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

Although not formally stated in the dossier, ECHA understands that you also sought to apply a read-across approach for information requirements for genotoxicity.

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[2]. 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.

[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.

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[3]- (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.

You consider to achieve compliance with the REACH information requirements for the registered substance a-methylcinnamaldehyde using data of the following structurally similar substances:

- Cinnamaldehyde (EC No. 203-213-9; CAS No. 104-55-2)
- trans-cinnamaldehyde (EC No. 604-377-8; CAS No. 14371-10-9)
- Alpha Hexyl Cinnamic Aldehyde (EC No. 202-983-3; CAS No. 101-86-0)
- Cinnamyl alcohol (EC No. 203-212-3; CAS No. 104-54-1)
- trans-Cinnamic acid (EC No.205-398-1; CAS No. 140-10-3)
- Benzoic acid (EC No.200-618-2; CAS No. 65-85-0)
- Amyl cinnamic aldehyde (EC No.800-696-3; CAS No.78605-96-6)

hereafter, as 'Source substances'

You have provided documentation of the read-across adaptation, but the documentation that you provided in your dossier does not contain any specific justification whereby relevant human health or ecotoxicological properties of the registered substance may be predicted from data for the Source substances. Specifically, your dossier does not address why such prediction would be possible.

ECHA notes that the two justification documents attached to Section 13 of IUCLID contain generic descriptions of the metabolism of cinnamic aldehyde derivatives and some data on cinnamic aldehyde on reproductive toxicity. They appear to be copied from the JECFA Report "*Cinnamyl alcohol and related flavouring agents*" (WHO FAS 46, 2000). They do not provide

[3] Please see ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

any hypothesis, data matrix and other information (e.g. rate of metabolism) and specific reasoning why a grouping and read-across approach according to the provisions laid down in Annex XI, Section 1.5. is possible for the registered substance.

In the absence of this information, ECHA cannot verify that the properties of the registered substance can be predicted from the data on the Source substances.

Hence, you have not established that relevant properties of the registered substance can be predicted from data on the Source substances. Since your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5., it is rejected and it is necessary to perform testing on the registered substance. 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.

In your comments to the draft decision you agree with ECHA that "*the information presented on read-across is not robust*". Irrespective of this, you still "*believe that the read-across is valid*" and you indicated that "*with focused efforts to update the dossier*" you claimed that you "*would be able to substantiate the read-across*". Hence, in your comments you requested "*ECHA to grant an opportunity [...] to update the dossier, to bring it in alignment with the expectations for a read-across approach*". However, ECHA notes that this decision does not take into account any updates submitted after 19 July 2018 as indicated in the draft decision notified to you. All the new information in the later update(s) of the registration dossier will be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation (after the deadline indicated in the adopted decision has passed).

ECHA has addressed your comments on the draft decision for the read-across approach under the relevant endpoint specific sections.

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 as laid down in Annex VII, Section 8.4.1. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA.

Other tests may be used if the conditions of Annex XI are met. More specifically, Section 1.1.2 of Annex XI provides that existing data on human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) may be used if the following conditions are met:

(1) Adequacy for the purpose of classification and labelling and/or risk assessment;
(2) Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) adequate and reliable documentation of the study is provided.

According to paragraph 13 of the current OECD TG 471 test guideline (updated 1997) at least five strains of bacteria should be used: *S. typhimurium* TA1535; TA1537 or TA97a or TA97; TA98; TA100; *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101). This includes four strains of *S. typhimurium* (TA1535; TA1537 or TA97a or TA97; TA98; and TA100) that have been shown to be reliable and reproducibly responsive between laboratories. These four *S. typhimurium* strains have GC base pairs at the primary reversion site and it is known that they may not detect certain oxidising mutagens, cross-linking agents and hydrazines. Such substances may be detected by *E. coli* WP2 strains or *S. typhimurium* TA102 which have an AT base pair at the primary reversion site.

You have provided the following study records with the registered substance:

i. A test from the year 1998 (publication data; Dillon et al.), not GLP compliant and no test guideline followed, with an assigned reliability score of 2. The test used three different strains of *S. typhimurium* TA 100, TA 102 and TA 104. The test did not include strains *S. typhimurium* TA1535; TA1537 or TA97a or TA97; TA98.
ii. A test from the year 1986 (publication data; Mortelmans et al.) no test guideline followed and not GLP compliant, with an assigned reliability score of 2. The test used four different strains of *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 and it did not include tests with strains *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101).
iii. Another test from the year 1983 (publication data; Wild et al.) no test guideline followed and not GLP compliant, with an assigned reliability score of 2. The test used four different strains of *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 and it did not include tests with strains *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101).

ECHA notes that none of the above mentioned studies follow test guidelines and they are not GLP compliant. Moreover, ECHA notes that no adequate and reliable documentation has been provided for the study records hence the validity of the studies cannot be assessed.

In your comments to the draft decision you refer to the key studies (i) and (ii), performed with the registered substance, arguing that "*all strains, recommended in the current OECD TG 471 guideline have been tested, albeit not in the same study*". Further, for the study record (ii) you provided tabulated data which was not part of the IUCLID entry for this study because the "*original article was truncated at page 55*". You further state that "*the full citations will be added to the endpoint records in IUCLID, and the endpoint records themselves will be updated to more robustly reflect the materials, methods and results described in the paper*".

As already mentioned above, ECHA notes that the study records do not provide information equivalent to the data generated by the corresponding test method (OECD TG 471) because you fail to provide adequate and reliable documentation. Therefore, the provided study records do not meet the current guidelines, nor can they be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation. ECHA notes that a robust study summary is required under Article 10(a)(vii). Hence, ECHA considers that the information provided in the endpoint study records do not meet the requirements of a robust study summary[4], as defined in Article 3(28) of the REACH Regulation.

[4] ECHA's practical guide for "*How to report robust study summaries*", available at: http://echa.europa.eu/documents/10162/13643/pg_report_robust_study_summaries_en.pdf.

ECHA notes, that for study record (i), as explained above you failed to provide adequate and reliable documentation. As regards study record (ii), you provided tabulated data in your comments. However, ECHA notes that there is no data with no metabolic activation at the two top concentrations ([redacted] and [redacted] mg/plate) as well as no data with metabolic activation for the concentration of [redacted] mg/plate.

ECHA aknowledges your intention to update your dossier "*to more robustly reflect the materials, methods and results described in the paper*". However, ECHA notes that you were informed in the notification letter to the draft decision, that ECHA will not take any updates into account for the current decision making.

In conclusion, the issues addressed above are not adequately addressed in your comments on the draft decision and in the technical dossier. Hence, ECHA notes that there is insufficient information in the technical dossier to make an independent assessment of the studies. For the reasons explained above, ECHA considers that, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that the bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. 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: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471).

2. 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 not provided any study record for an *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study in the dossier that would meet the information requirement of Annex VIII, Section 8.4.2.

You did not provide any justification for adaptation of the information requirement for this endpoint, according to Column 2, Section 8.4.2 of Annex VIII or Annex XI, section 1.5 and/or 1.2.

In the IUCLID dossier (7.6.2. Genetic toxicity in vivo) you have provided the following information with the registered substance:

iv. Study record for *in vivo* cytogenicity key study (Mouse bone marrow micronucleus test) (publication data: Wild et al. 1983). The study is not GLP compliant and no test guideline was followed; an assigned reliability score of 2.

v. Study record for *in vivo* gene mutation supporting study (Drosophila SLRL assay) (publication: Wild et al. 1983). The study is not GLP compliant and no test guideline was followed; an assigned reliability score of 2.

Additionally, with the source substance amyl cinnamic aldehyde (EC: 800-696-3) you have provided:

vi. Study record for *in vivo* gene mutation supporting study (Drosophila SLRL assay) (publication: Wild et al. 1983). The study is not GLP compliant and no test guideline was followed; an assigned reliability score of 2. You flagged the study as "read-across".

Based on the study records you have provided, ECHA understands that you sough to adapt this information requirement according to Column 2, Section 8.4.2 of Annex VIII and Annex XI, sections 1.1 and 1.5.

ECHA notes that the mouse bone marrow micronucleus test (study record iv.) is briefly reported in a publication which investigates 76 artificial flavouring substances for potential mutagenic properties. The study is not GLP compliant and does not follow the current guideline OECD TG 474, more specifically, the test is performed in only 4 animals (the sex is not clear), while according to the OECD TG 474 guideline, "*at least 5 animals per sex*" have to be used. There is no data on the frequency of the treatment and there is no information on the criteria for dose selection, as well as on the positive control(s) used. In the study summary there is no explanation why the highest dose used was 438 mg/kg bw and there is no data on whether a range-finding study has been performed. No details on the results obtained are presented in tabulated form in the study summary. Further, there is no proof of bone marrow exposure that would enable to validate the negative results. Therefore, ECHA considers that there is insufficient information to make an independent assessment of the study and the study does not appear to cover the key parameters foreseen for the relevant study. Hence, the adaptation of Annex VIII, Section 8.4.2., column 2, cannot be applied in this case since the *in vivo* cytogenicity study available in the technical dossier is not considered as "*adequate data*".

Further, the study records (v.) and (vi.) do not provide information on *in vitro* cytogenicity in mammalian cells. Hence, it is not relevant for the assessment of this standard information requirement as per Annex VIII, Section 8.4.2.

In your comments to the draft decision you agreed to perform the study. However, you also stated that "*the existing data (despite limitations) are adequate*".

ECHA notes that in your comments you agreed that "*the Wild et al. (1983) study* [study record (iv)] *(the mouse bone marrow study mentioned by ECHA) lacks detail*". ECHA further notes that for this study you addressed only one of the shortcomings, namely that "*only 4 animals (the sex is not clear)*" were used. However, you did not address the other shortcomings addressed above.

Furthermore, in your comments under this endpoint you say "*While there was no in vitro cytogenicity test with the target substance, there are a wealth of both in vitro and in vivo cytogenicity studies with cinnamyl derivatives*". You also provide a table, summarising the *in vitro* and *in vivo* cytogenicity studies performed with different cinnamyle derivatives. Finally, you concluded that on the basis of a weight of evidence from this data "*the cinnamyl derivatives do not present a risk of causing chromosomal aberrations*".

ECHA notes that in your comments you have sought to adapt this information requirement according to Annex XI, Section 1.2., weight of evidence. However, you did not provide an explanation or justification on how these sources of information/studies, enable an assumption or conclusion that the registered substance does or does not have a dangerous (hazardous) property with respect to chromosome aberration. Moreover, ECHA points out that this data, with the various analogue substances, is not presented in the current dossier. Hence, the weight of evidence adaptation cannot be accepted as you failed to provide adequate and relaibliable documentation.

Moreover, as mentioned above in Appendix 1, under the "Grouping and read-across approach for toxicological information" of this decision, currently your read-across approach is rejected.

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

ECHA considers that the *in vitro* mammalian chromosome aberration test (test method 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).

3. 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 both studies requested under 1. and 2. have negative results.

You did not provide any justification for adaptation of the information requirement for this endpoint, according to Column 2, Section 8.4.3. of Annex VIII or Annex XI, section 1.5 and/or 1.2.

In the IUCLID dossier (7.6.2. Genetic toxicity in vivo) you have provided the study records (iv), (v) and (vi), listed above in section 2, Appendix 1 of this decision.

Based on the study records you have provided, ECHA understands that you sough to adapt this information requirement according to Column 2, Section 8.4.3. of Annex VIII and according Annex XI, Section 1.5.

ECHA notes that the study (iv) with the registered substance does not provide information on

in vitro gene mutation in mammalian cells. Hence, it is not relevant for the assessment of this standard information requirement as per Annex VIII, Section 8.4.3.

ECHA further notes that you have provided a Drosophila SLRL assay both for the registered and the source substance amyl cinnamic aldehyde (EC No. 800-696-3) (publication: Wild et al., 1983). As specified in the test guidelines for *in vivo* gene mutation investigation (OECD TG 488 and TG 489, the *in vivo* studies referred to in Annex VIII, section 8.4.3., column 2, should be performed on rodents or other species with the most relevant metabolism for humans. Since this study has been performed on insects, which metabolism differs to the one of humans, it is not considered as being acceptable and the adaptation of Annex VIII, Section 8.4.3., column 2, cannot be applied.

Further, as explained above in Appendix 1, "Grouping and read-across approach for toxicological information" of this decision, your adaptation of the information requirement is rejected.

In your comments to the draft decision you referred to the WHO FAS 46 (2000) report and indicated that "*it is clear that the cinnamyl derivatives overall lack information on in vivo mammalian mutation*". You also claimed that " [...] *this lack of specific data is related to the fact that the overall Weight of Evidence approach taken in these reviews by other regulatory bodies did not identify genotoxicity as a concern*". You stated that the "*overall weight of evidence provides a picture that the cinnamyl derivatives do not present a risk of causing mutations*".

As explained above you have not provided any gene mutation study in mammalian cells study to fulfill the standard information requirement for this endpoint. Hence, you did not provide "*several independent sources of information*" to support your weight of evidence approach indicated in your comments.

With reference to your comment "*other regulatory bodies did not identify genotoxicity as a concern*". ECHA notes that it is entirely possible that ECHA and other bodies would come to different actions as a result of the different tasks they perform. During a compliance check, ECHA must ensure that the information present in the registration dossier corresponds to specific information requirements of the REACH Regulation.

In view of the above, ECHA considers that the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

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

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 both studies requested under 1. and 2. have negative results.

4. 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. No such evidence is presented in the dossier. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation.

In the IUCLID dossier you have provided the following study records relevant for this endpoint, with the source substances, as follow:

with alpha hexyl cinnamic aldehyde (EC No. 202-983-3)

- One-Generation reproduction toxicity study (GLP compliant, OECD TG 415) via oral-gavage in rats at doses: 0, 12.5, 25, 50, 100 mg/kg bw/day ([redacted] 2010), with assigned reliability score of 1. NOAEL = 100 mg/kg bw/day

With benzoic acid (EC No. 200-618-2)

- One-generation reproduction toxicity study (no GLP compliant, no Guideline) in female hamsters, treated via oral-gavage between 6-10 GD, at doses: 0, 6, 30, 60, 600 mg/kg bw/day ([redacted] 2001), with assigned reliability score of 2. NOEL for F1 = 60 mg/kg bw/day based on "*A significant number of resorptions was noted in hamsters which received /greater than or equal to/ 30 mg/kg. The incidence of fetal malformations achieved statistical significance at >600 mg/kg*".

- One-generation reproductive toxicity study (no GLP compliant, no Guideline) in female rats, treated via oral-gavage between 6-15 GD, at doses: 0, 5, 25, 50, 500 mg/kg bw/day ([redacted] 2001), with assigned reliability score of 2. NOEL for both maternal and reproductive toxicity = 500 mg/kg bw/day

- Multi-generation reproductive toxicity dietary study (no GLP compliant, no Guideline), in rats, concentration in feed: up to 1% (app. 500 mg/kg bw/day) (W. Kiekebusch and K. Lang 1960), with assigned reliability score of 2. NOEL = 500 mg/kg bw/day

Further, you have provided a QSAR prediction for the reproductive toxicity endpoint for trans-alpha-methyl cinnamic aldehyde (CAS No. 101-39-3) by means of Derek Nexus 2.0.3. You state that no structural alerts for reproductive and/or developmental toxicity are found.

As explained above in Appendix 1, "Grouping and read-across approach for toxicological information" of this decision, your adaptation of the information requirement is rejected.

ECHA further notes that you have flagged these studies as Weight of evidence. However, you did not provide any justification on how the information obtained from these studies would contribute to a weight of evidence approach (in addition to the grouping and read-across approach already assessed above) to determine whether the registered substance has or has

not a dangerous property for the information requirement under consideration.

In your comments on the draft decision you agreed that the read-across approaches as given in the technical dossier were not robust, however you considered the read-across is still possible and have, in your comments, provided further justification.

For the analogue substance (alpha hexyl cinnamic aldehyde) you provided new identifiers (CAS: 165184-98-5 and EC: 639-566-4) and the information that the substance was "*primarily a cis-enantiomer*". You indicated that both the target and the analogue substances are structurally similar and they both metabolise by beta-oxidation (prediction using OECD QSAR Toolbox v4.1). You further stated that "*The similarity in structure and function was the basis for both the WHO Joint Evaluation Committee for Flavoring Additives (WHO FAS 46, 2000) and European Food Safety Authority (EFSA, 2009) to evaluate both of (2E)-2-methyl-3-phenylacrylaldehyde and (2E)-2-(phenylmethylidene)octanal*" and that "*Overall, ECHA's rejection of read-across to of (2E)-2-(phenylmethylidene)octanal (commonly known as alfa-hexylcinnamaldehyde) is in disagreement with the approach taken by both WHO/JECFA and EFSA*".

As already explained above in Appendix 1, "Grouping and read-across approach for toxicological information" of this decision, currently your read-across approach is rejected.

ECHA can already point out that the registered and the analogue substance differ in structure. You did not explain why the additional C-5 aliphatic group in the analogue substance would not affect the toxicological profile of the analogue and the registered substances. Further, ECHA notes that the predicted metabolites of the registered and the analogue substance also differ. You did not comment on those differences and did not explain how those differences would affect the toxicological profile of both substances. Therefore, ECHA considers that you failed to provide enough arguments to support your read-across approach for the property: reproductive toxicity.

In your comments you also refer to the different approach on read-across taken by ECHA and by WHO/JECFA and EFSA. ECHA notes that different bodies may come to different actions as a result of the different tasks they perform.

For the reasons 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.

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, December 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 (https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf) Section R.7.6.2.3.2., pages 484 to 485 of version 6.0 – July 2017.

5. 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 as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation.

In the IUCLID dossier, you have provided the following study record for the target substance:

- Sub-chronic (90-day) toxicity dietary study in rats. Doses: 0, 58, 120, 220 mg/kg/bw/day ([redacted] 1958a), with assigned reliability score of 2. The study is no GLP compliant and pre-Guideline. NOAEL = 220 mg/kg/ bw/day

ECHA notes that you have assigned a reliability score of 2. ECHA does not agree with the reliability score, since the study is performed in 1958; the study was not conducted according to GLP; and it does not cover all the key parameters foreseen to be investigated in the current OECD TG 408 (updated 2017), such as behavioral observation battery, endocrine effects etc. Therefore, the study is not acceptable to meet the information requirements according Annex IX, Section 8.6.2.

In the IUCLID dossier, you have provided the following study records with the source substances, as follow:

With cinnamaldehyde (EC No. 203-213-9):

- Short-term (14-day) oral-gavage study (no GLP compliant, no Guideline) in rats, administered via oral-gavage at 0, 235, 470, 940, 1880, 3750 mg/kg bw/day (nominal) or microencapsulated in feed at concentrations: 0, 0.625, 1.25, 2.5, 5, or 10% (equivalent to app. 0, 188, 375, 750, 1500, 3000 mg/kg bw/day) (Hébert,et al., 1994). You have assigned a reliability score of 1. NOAEL via oral-gavage = 235 mg/kg bw/day based on forestomach hyperplasia observed in animals treated at 470

mg/Kg/day and higher. NOAEL via microencapsulated feed = 1500 mg/Kg bw/day, based on effects observed on reproductive organs and secondary sex glands (seminal vesicles and prostates of males; ovaries and uteri of females).

- Short-term (14-day) oral-gavage study (no GLP compliant, no Guideline followed) in mice, administered via oral-gavage at 0, 656, 1310, 2620, 5250, 10500 mg/kg bw/day (nominal) or microencapsulated in feed at concentrations: 0, 0.625, 1.25, 2.5, 5, or 10% (equivalent to app. 0, 474, 948, 1875, 3750, 7500 mg/kg bw/day) (Hébert,et al., 1994). You have assigned a reliability score of 1. NOAEL oral-gavage = 1310 mg/kg bw/day based on mortality observed at 2620 mg/kg bw and above. NOAEL via microencapsulated feed = 1875 mg/kg based on a dose-related increase in uterine hypoplasia observed in female mice.
- Sub-chronic (16 week) toxicity study (no GLP compliant, no Guideline followed) in rats, fed at concentrations of 0, 1000, 2500, 10000 ppm (equivalent to app. 50, 120, 500 mg/kg bw/day) (Hagan et al., 1967). You have assigned a reliability score of 2. NOEL = 2500 ppm based on slight hepatic cellular swelling and slight hyperkeratosis of the squamous.
- Sub-chronic (12 weeks) toxicity study (no GLP compliant, no Guideline followed) in rats, est. daily intake in feed: 50, 100, 200 mg/kg) ([redacted] 1958b). You have assigned a reliability score of 2. NOAEL = 200 mg/kg bw/day.

with trans-cinnamaldehyde (EC No. 604-377-8):

- Sub-chronic (90-day) toxicity study (GLP compliant; OECD TG 408) in rats, administered microencapsulated in feed at 4100, 8200, 16500, 33000 ppm (equivalent app. to 275, 625, 1300, 4000 mg/kg bw/day for males and 300, 570, 1090, 3100 mg/kg bw/day for females) (NTP 2004). You have assigned a reliability score of 1. The study does not set up any NO(A)EL value. It is a dose range-finding study for the 2-year study. The observed effects: reduced body weights, decreased feed consumption, and increased incidences and severities of forestomach lesions.
- Sub-chronic (90-day) toxicity study (GLP compliant; OECD TG 408) in mice, administered microencapsulated in feed at 4100, 8200, 16500, 33000 ppm (equivalent app. to 650, 1320, 2550, 5475 mg/kg bw/day for males and 625, 1380, 2680, and 5200 mg/kg bw/day for females) ([redacted] 2004). You have assigned a reliability score of 1. The LOAEL = 4100 ppm (650 mg/kg bw) based on reduced body weight in male rats. A NOAEL could not be determined in this study.
- Oral combined chronic repeated dose/carcinogenicity study (similar or equivalent to OECD TG 453, GLP not specified) in rats, administered microencapsulated in the feed at concentrations: 0, 1000, 2100, 4100 ppm (equivalent app. to 0, 50, 100, 200 mg/kg for M/F) ([redacted] 2004). You have assigned a reliability score of 1. NOAEL non neoplastic = 100 mg/kg bw/day based on decreased BW at 200 mg/kg bw/day. NOAEL neoplastic = 200 mg/kg bw/day (HDT).
- Oral combined chronic repeated dose/carcinogenicity study similar or equivalent to OECD TG 453, GLP not specified) in mice, administered microencapsulated in the feed at concentrations: 0, 1000, 2100, 4100 ppm (equivalent app. to 0, 125, 270, 540 for males or 570 mg/Kg for females) ([redacted] 2004). You have assigned a reliability score of 1. NOAEL non-neoplastic = 125 mg/kg bw/day, based on decreased BW at 270 mg/kg bw/day and above. NOAEL neoplastic = 540 mg/kg bw/day (HDT).

with amyl cinnamic aldehyde (EC No. 800-696-3):

- Sub-chronic (90-day) toxicity study (no GLP compliant, pre-Guideline) in rats, fed at 0, 80, 400 4000 ppm (equivalent app. to 6.1/6.7, 30/35, 290/320 mg/kg bw/day M/F) (Carpanini et al., 1973). You have assigned a reliability score of 2. NOAEL = 30/35 mg/kg bw/day M/F, based on vacuolation of some liver cells, protein casts in the kidney tubules and signs of chronic lung infection
- Sub-chronic (12 weeks) toxicity study (no GLP compliant, pre-Guideline) in rats, fed at concentration of 2% (equivalent to 6.1 mg/kg bw for males and 6.6 mg/kg bw for females) mixed in cotton seed oil (Oser et al., 1965). You have assigned a reliability score of 2. NOAEL = 6.1/6.6 mg/kg bw (M/F)

with alpha hexyl cinnamic aldehyde (EC No. 202-983-3):

- Short-term (14-day) toxicity study (GLP compliant, no Guideline) in rats, administered via oral-gavage with 0, 100, 250, 500, 1000 mg/kg bw/day ([redacted] 2004). You have assigned a reliability score of 1. NOAEL = 500 mg/kg bw/day based on mortality and adverse affects (net body weight loss, decreased food consumption, substance-related histopathological changes in the kidneys and in the stomach).

ECHA notes, that most of the source studies for which you have applied a reliability scores of 1 or 2, are no GLP compliant and pre-Guideline or no specific Guideline was followed. Based on this, ECHA does not agree with the assigned study reliabilty. Moreover, the study design and the evaluated parameters do not cover all the key parameters foreseen to be investigated in the current OECD TG 408 (updated 2017).

Therefore, ECHA concludes that the source studies, do not provide the information required by Annex IX, Section 8.6.2., because they do not meet the requirements of Annex XI, Section 1.1.2. and Annex XI 1.5.

Additionally, as explained above in Appendix 1, "Grouping and read-across approach for toxicological information" of this decision, your adaptation of the information requirement is rejected.

ECHA further notes that you have flagged the above mentioned studies as Weight of evidence. However, you did not provide any justification on how the information obtained from these studies would contribute to a weight of evidence approach (in addition to the grouping and read-across approach already assessed above) to determine whether the registered substance has or has not a dangerous property for the information requirement under consideration.

In your comments to the draft decision you agreed that the read-across approaches as given in the technical dossier were not robust, however you considered that the read-across is still possible. For this endpoint you further stated that "*there are multiple repeated-dose studies for multiple source substances, which when taken together form a strong Weight of Evidence argument that the endpoint has indeed been met*".

ECHA notes that in your comments you provided the summarised information (in tabulated form) for the studies which you have already provided in the registration dossier and ECHA has evaluated (see above). Further, ECHA notes that your statement that this information "*taken together form a strong Weight of Evidence argument*" has not been justified with any new arguments how the information obtained from these studies would contribute to a weight

of evidence approach (in addition to the grouping and read-across approach) to determine whether the registered substance has or has not a dangerous property for the information requirement under consideration.

Moreover, in regard to the 90-day study with the registered substance ([redacted] 1958a) you disagree with ECHA's comments on the reliability of the study. You argue that "*the registrant's selection of reliability scores is in alignment with the approach taken by both WHO/JECFA*".

However, ECHA notes that in your dossier and in your comments you did not provide a robust information for this study. Therefore, the provided 90-day study record with the registered substance does not meet the current guidelines, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation. ECHA notes that a robust study summary is required under Article 10(a)(vii). Hence, ECHA considers that the information provided in the endpoint study records does not meet the requirements of a robust study summary[5], as defined in Article 3(28) of the REACH Regulation.

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

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance is a liquid of very low vapour pressure. Uses with industial spray application (PROC 7) are reported in the chemical safety report. However, the reported concentrations are low ([redacted]%).

Hence, the test shall be performed by the oral route using the test method OECD TG 408.

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

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Repeated dose 90-day oral toxicity study (test method: OECD TG 408) in rats.

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

A "pre-natal developmental toxicity study" (test method 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

[5] ECHA's practical guide for "*How to report robust study summaries*", available at: http://echa.europa.eu/documents/10162/13643/pg_report_robust_study_summaries_en.pdf.

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. In the IUCLID dossier you have provided the following study records relevant for this endpoint, with the source substances, as follow:

With Benzoic acid (EC No. 200-618-2)

- One-generation reproduction toxicity study (no GLP compliant, no Guideline followed) in female hamsters, treated via oral-gavage between 6-10 GD, at doses: 0, 6, 30, 60, 600 mg/kg bw/day ([redacted] 2001). You have assigned reliability score of 2. NOEL for F1 = 60 mg/kg bw/day based on "*A significant number of resorptions was noted in hamsters which received /greater than or equal to/ 30 mg/kg. The incidence of fetal malformations achieved statistical significance at >600 mg/kg*".

- One-generation reproductive toxicity study (no GLP compliant, no Guideline followed) in female rats, treated via oral-gavage between 6-15 GD, at doses: 0, 5, 25, 50, 500 mg/kg bw/day ([redacted] 2001). You have assigned reliability score of 2. NOEL for both maternal and reproductive toxicity = 500 mg/kg bw/day

With cinnamaldehyde (EC No. 203-213-9):

- Developmental toxicity dietary study (no GLP compliant, no Guideline followed) in CD 1 mice, fed with the substance at nominal dose of 1200 mg/kg bw/day (nominal) ([redacted] 1989). You have assigned a reliability score of 2. NOAEL = 1200 mg/kg bw/day

- Teratogenicity study in SD rats (no GLP compliant, no Guideline followed), the substance administered via oral-gavage at 5, 25 and 250 mg/kg bw/day during 7-17 GD (Mantovani, A. et al. 1989). You have assigned a reliability score of 3. LOAEL developmental toxicity = 5 mg/kg bw/day based on increased incidence of poor cranial ossification, decreased ossification of tympanic bulla, increased incidence of dilated pelvis/reduced papilla in kidney, dilated ureter; NOAEL maternal toxicity = 250 mg/kg bw/day

- Developmental toxicity study in CD 1 mice (no GLP compliant, no Guideline followed), the substance administered via oral-gavage (Hardin et al., 1987). Reliability 2, no guideline, no GLP. The study was conducted in two phases: initial dose finding study followed by a reproductive phase, which employed a single dose level of 1200 mg/kg bw/day. NOEL = 1200 mg/kg bw/day

With Cinnamyl alcohol (EC No. 203-212-3) and Trans-Cinnamic acid (EC No. 205-398-1)

- Developmental toxicity study in rtas (no GLP compliant, no Guideline followed), administered cinnamyl alcohol at a single dose of 53.5 mg/kg bw/day and trans-cinnamic acid at 50 mg/kg bw/day during the entire pregnancy (Zaitsev et al, 1975). You have assigned a reliability score of 2. Route of administration is not specified. No effects reported.

- Developmental toxicity study in rats (no GLP compliant, no Guideline followed), administered cinnamic alcohol on day 4 (implantation) or 10-12 GD at dose of 53.5 mg/kg bw/day (Zaitsev & Magranova, 1973). You have assigned a reliability score of 2. Route of administration is not specified. NOAEL = 53.5 mg/kg bw/day

Further, you have provided a QSAR prediction for the reproductive toxicity endpoint for trans-alpha-methyl cinnamic aldehyde (CAS No. 101-39-3) by means of Derek Nexus 2.0.3. You state that no structural alerts for reproductive and/or developmental toxicity are found.

ECHA notes, that most of the source studies for which you have applied a reliability scores of 1 or 2, are no GLP compliant and pre-Guideline or no specific Guideline was followed. Based on this, ECHA does not agree with the assigned study reliability. Moreover, the study design and the evaluated parameters do not cover all the key parameters foreseen to be investigated in the current OECD TG 414.

Therefore, ECHA concludes that the source studies, do not provide the information required by Annex IX, Section 8.6.2., because they do not meet the requirements of Annex XI, Section 1.1.2. and Annex XI 1.5.

Additionally, as explained above in Appendix 1, "Grouping and read-across approach for toxicological information" of this decision, your adaptation of the information requirement is rejected. ECHA further notes that you have flagged these studies as Weight of evidence. However, you did not provide any justification on how the information obtained from these studies would contribute to a weight of evidence approach (in addition to the grouping and read-across approach already assessed above) to determine whether the registered substance has or has not a dangerous property for the information requirement under consideration.

In your comments to the draft decision you agreed that the read-across approach as given in the technical dossier was not robust, however you still consider that the read-across is possible. Further, you consider that based on weight of evidence "*this endpoint has been adequately met*".

ECHA notes that in your comments you copied from the WHO/JECFA report the summaries for the studies with cinnamaldehyde, cinnamyl alcohol and cinnamic acid. However, you did not justify with any new arguments how the information obtained from these studies would contribute to a weight of evidence approach (in addition to the grouping and read-across approach) to determine whether the registered substance has or has not a dangerous property for the information requirement under consideration.

Finally, ECHA notes that as mentioned above in Appendix 1, "Grouping and read-across approach for toxicological information" of this decision, currently your read-across approach is rejected.

For the reasons explained above, ECHA considers that 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 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: OECD TG 414) in a first species (rat or rabbit) by the oral route.

7. Robust study summary for "Algae, Growth Inhibition Test According to OECD 201 (March 23, 2006)" (Annex VII, Section 9.1.2. in conjunction with Annex I, Section 3.1.5.)

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

A growth inhibition study with aquatic algae is a standard information requirement as laid down in Annex VII, Section 9.1.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement. Furthermore, pursuant to Article 10 (a)(vii) and Annex I, Section 3.1.5. where there is more than one study addressing the same effect, then the study or studies giving rise to the highest concern shall be used to draw a conclusion and a robust study summary (RSS) shall be prepared for that study or studies and included as part of the technical dossier. Robust summaries will be required of all key data used in the hazard assessment.

You have provided a study record for an *"Algae, Growth Inhibition Test According to OECD 201 (March 23, 2006)"* [redacted] to meet the standard information requirement of Annex VII, Section 9.1.2.

However, ECHA notes that, contrary to Article 3(28) of the REACH Regulation, reporting the results of this study in the robust study summary is not adequate for its use in hazard assessment. In particular, you report the effect values based on the nominal concentrations while you note in the full study report and in your robust study summary that the concentrations of the test item have not been maintained within the [redacted]% of the nominal values.

According to OECD TG 201, if the concentration of the substance being tested is not within the range of [redacted] % from the nominal or measured initial concentration, analysis of the results should be based on geometric mean concentration during exposure or on models describing the decline of the concentration of the test substance. Even though not used in the chemical safety assessment, you have calculated the EC50 values also with the geometric mean exposure concentrations. For the Growth Rate ErC50 (analysed) was 0.39 mg/L. Based on nominal concentrations the effect value you reported and used in the chemical safety assessment is ca 14.8 mg/L, which indicates that the concentrations have not been maintained within the [redacted]% of the nominal.

Therefore, you need to provide a revised robust study summary considering the above elements in your robust study summary for this study. In particular, as required in OECD TG 201 you need to report the effect concentrations based on geometric mean concentration during exposure or on models describing the decline of the concentration of the test substance, in case the concentrations measured in monitoring are not within the [redacted]% of the nominal concentrations. You shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation.

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

In your comments on the draft decision you agreed to update the RSS as requested and to use measured concentrations to report the EC50. You agree also to subsequently update the hazard and exposure assessment.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information: Revised robust study summary for the *"Algae, Growth Inhibition Test According to OECD 201 (March 23, 2006)"* [redacted].

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

"Short-term toxicity testing on fish" is a standard information requirement as laid down in Annex VIII, Section 9.1.3. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation. In the IUCLID dossier you have provided the following study record relevant for this endpoint, with the source substance α-hexylcinnamaldehyde (CAS No 101-86-0, EC No 202-983-3): Fish, Acute Toxicity Test according to OECD TG 203 (GLP compliant, with Pimephales promelas, 96-h LC50 1.7mg/L, meas.), [redacted] 2010.

As explained above in Appendix 1, "Grouping and read-across approach for toxicological and ecotoxicological information" of this decision, your adaptation of the information requirement is rejected.
In your comments on the draft decision (DD) you agree that the read-across approach as given in the technical dossier was not robust, however you consider the read-across still

possible and have, in your comments, provided further justification. ECHA has assessed the information presented in your comments according to Annex XI, section 1.5. grouping of substances and read-across approach.

You indicate that both substances "*contain the same core structure (benzyl group, with a branched aliphatic, aldehydic moiety), with α-Hexylcinnamaldehyde containing an additional C-5 aliphatic group at the 2-methyl carbon of (2E)-2-methyl-3-phenylacrylaldehyde*". You also indicate that "*the main difference is the increase in the Log Kow that corresponds to an increase in the carbon chain length in the source substance*". You explain that the substances have similar toxic potency but "*there is a positive correlation between the hydrophobicity of a substance in this group and its acute toxicity*". As the source substance is more hydrophobic you consider a read-across from the source to the target "*reasonable and conservative*". ECHA considers this as your updated read-across hypothesis.

To support your hypothesis you have provided a data matrix of selected physicochemical and environmental fate properties. ECHA notes that while the substances water solubilities (target 0.49 g/L, source 0.00162 g/L) and partitioning coefficients (target Log Kow 2.471, source Log Kow 5.3) differ, ECHA agrees that these observed differences relate to the difference in the chain length.

You have also provided another data matrix containing results of toxicity studies to algae and acute toxicity to invertebrates for both the target and the source. You indicate that "*these data show that the source substance has a higher toxicity to both algae and daphnia compared to the target substance*". You conclude that based on the data provided "*reading across from the source substance fish data to the target substance would be reasonable as a conservative assessment*".

ECHA agrees that the ecotoxicity study results provided in your comments support your hypothesis that the toxicity incerases with chain length and increasing log Kow. However, as the algae and daphnia studies on the source substance are not available in the registration dossier ECHA cannot verify the reliability of these studies.

Regarding characterisation of the source substance and in particular the test material used in the short-term fish study, ECHA notes that you have not provided any information on the purity and potential impurities. The substance characterisation of the source substance would need to be sufficiently detailed in order to assess whether the attempted prediction is not compromised by the composition and/or impurities. In the ECHA practical guide 6 "How to report on Read-Across" it is recommended to follow the ECHA Guidance for identification and naming of substances under REACH and CLP (version 1.3, February 2014) also for the source substances. This ensures that the identity of the source substance and its impurity profile allows an assessment of the suitability of the substances for read-across purposes.

Overall, ECHA considers that based on the information provided in your comments the read-across approach for the current endpoint seems plausible. However the justification, together with any other supporting evidence, would need to be included in the technical dossier. At the follow up stage ECHA will assess the updated dossier and any relevant documentation therein.

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

According to ECHA *Guidance on information requirements and chemical safety assessment,* Chapter R.7b (version 4.0, June 2017) fish acute toxicity test (test method EU C.1. / OECD TG 203) is the preferred test to cover the standard information requirement of Annex VIII, Section 9.1.3.

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: Fish, acute toxicity test (test method: EU C.1./OECD TG 203).

9. 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 as laid down in Annex IX, Section 9.1.5. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex IX, Section 9.1.5., column 2. You provided the following justification for the adaptation:

"In Annex IX of Regulation (EC) No 1907/2006, it is laid down that long-term toxicity tests shall be proposed by the registrant if the chemical safety assessment indicates the need to investigate further the effects on aquatic invertebrates. According to Annex I of this regulation, the chemical safety assessment triggers further action when the substance or the preparation meets the criteria for classification as dangerous according to Directive 67/548/EEC or Directive 1999/45/EC or is assessed to be a PBT or vPvB. The hazard assessment of Cyprinal reveals neither a need to classify the substance as dangerous to the environment, nor is it a PBT or vPvB substance, nor are there any further indications that the substance may be hazardous to the environment. Therefore long-term toxicity testing in Daphnia magna is not provided."

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.5., column 2. Firstly, the information submitted for Growth inhibition study on aquatic algae (request 7) and Short-term toxicity testing on fish (request 8) is not currently compliant. Therefore the hazard assessment and Chemical Safety Assessment (CSA) described in Annex I cannot yet be concluded and used as an argument to adapt any further information requirements. The CSA shall consider PBT/vPvB assessment and environmental hazard assessment, including classification and labelling in accordance with Directive 67/548/EEC and identification of the Predicted No-Effect Concentration (PNEC) for risk assessment.
Secondly, ECHA notes that your argument that there are no indications that the substance may be hazardous to the environment is not correct. In contrast, as described in request 7, the registered substance seems toxic to aquatic algae with effect concentrations below 1 mg/L.

Therefore, your adaptation of the information requirement cannot be accepted.

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

In your comments to the draft decision you indicated that you would consider the need for the long-term daphnia study following the update of the RSS for the algae study (request 7.) and the subsequent update of the hazard and exposure assessment. You indicate that if further data is required you would either use read-across from α-hexylcinnamaldehyde or commission an OECD TG 211 study on the registered substance. ECHA agrees that you may first fulfil the information requirements for short-term aquatic endpoints and after the update of the Chemical Safety Report assess whether long-term testing is required. While no concrete read-across is yet proposed here, ECHA wants to higlight that if you wish to pursue a read-across approach in the future to fulfil this information requirement also, 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. Any study to be read-across also needs to be valid and sufficient information needs to be provided in a form of a robust study summary for ECHA to be able to assess its validity.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) *Daphnia magna* reproduction test (test method EU C.20. / OECD TG 211) is the preferred test to cover the standard information requirement of Annex IX, Section 9.1.5.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Daphnia magna reproduction test (test method: EU C.20./OECD TG 211).

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

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

You have sought to adapt this information requirement according to Annex IX, Section 9.1.6., column 2. You provided the following justification for the adaptation:
"*In Annex IX of Regulation (EC) No 1907/2006, it is stated that long-term toxicity tests shall be proposed by the registrant if the chemical safety assessment indicates the need to investigate further the effects on fish. According to Annex I of this regulation, the chemical safety assessment triggers further action when the substance or the preparation meets the criteria for classification as dangerous according to Directive 67/548/EEC or Directive 1999/45/EC or is assessed to be a PBT or vPvB. The hazard assessment of Cyprinalreveals neither a need to classify the substance as dangerous to the environment, nor is it a PBT or vPvB substance, nor are there any further indications that the substance may be hazardous to the environment. Therefore for the reasons above and for reasons of animal welfare long-term toxicity testing in fish is not provided.*"

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.5., column 2, due to reasons described in request 9 of this decision.

Therefore, your adaptation of the information requirement cannot be accepted.

In your comments to the draft decision you indicated that you would follow a stepwise approach whereby you would first fulfill the information requirements for short-term aquatic toxicity and subsequently refine yor hazard and exposure assessment. If long-term aquatic testing would then still be required you would first fulfil the information requirement for long-term aquatic invertebrates study and as a last point consider whether long-term fish testing is required. ECHA agrees that you may follow such approach as explained in the *Notes for your consideration* section at the end of this request.

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 ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) fish early-life stage (FELS) toxicity test (test method OECD TG 210), fish short-term toxicity test on embryo and sac-fry stages (test method EU C.15. / OECD TG 212) and fish juvenile growth test (test method EU C.14. / OECD TG 215) can be performed to cover the standard information requirement of Annex IX, Section 9.1.6.

However, the FELS toxicity test according to OECD TG 210 is more sensitive than the fish, short-term toxicity test on embryo and sac-fry stages (test method EU C.15 / OECD TG 212), or the fish, juvenile growth test (test method EU C.14. / OECD TG 215), as it covers several life stages of the fish from the newly fertilized egg, through hatch to early stages of growth (see ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), *Chapter R7b, Section R.7.8.4.1.*

Moreover, the FELS toxicity test is preferable for examining the potential toxic effects of substances which are expected to cause effects over a longer exposure period, or which require a longer exposure period of time to reach steady state (ECHA *Guidance Chapter R7b,* version 4.0, June 2017).

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

Notes for your consideration for the requests 7 to 10

ECHA notes that there are no reliable short-term studies available for some of the trophic levels as described in requests 7 and 8 of this decision. Therefore the Integrated testing strategy (ITS) outlined in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Section R.7.8.5, cannot be currently applied and the long-term studies on both invertebrates and fish are requested to be conducted (requests 9-10).

However, once results of the requested tests 7-8 are available, you shall revise the chemical safety assessment. Subsequently you shall consult the above mentioned ECHA *Guidance* Chapter R.7b to determine if long-term toxicity testing (requests 9-10) is necessary and the sequence in which the aquatic long-term toxicity tests are to be conducted.

According to above mentioned ECHA *Guidance* Chapter R.7b, if there is compelling evidence that neither fish nor invertebrates are shown to be substantially more sensitive, long-term studies may be required on both. In such case, according to the ITS, the *Daphnia* study is to be conducted first. If based on the results of the long-term *Daphnia* study and the application of a relevant assessment factor, no risks are observed (PEC/PNEC<1), no long-term fish testing may need to be conducted. However, if a risk is indicated, the long-term fish study needs to be conducted. If on the other hand there is compelling evidence to suggest that the fish/invertebrates is likely to be at least a factor of about 10 less sensitive than the other trophic levels there are no requirements for further testing on the least sensitive trophic level.

11. Short-term toxicity to terrestrial invertebrates (Annex IX, Section 9.4.1.), or Short-term toxicity to plants (Annex IX, Section 9.4.3.)

"Effects on terrestrial organisms" is a standard information requirement as laid down in Annex IX, Section 9.4. of the REACH Regulation. Adequate information on effects on short-term toxicity to invertebrates (Annex IX, Section 9.4.1.), effects on soil micro-organisms (Annex IX, Section 9.4.2.), and short-term toxicity to plants (Annex IX, Section 9.4.3.) needs to be present in the technical dossier for the registered substance to meet the information requirements.

You have waived the standard information requirements of Annex IX, Section 9.4. using the following justifications:
"*In accordance with column 2 of REACH Annex X, the long term toxicity testing* [*on invertebrates/plants*] *study does not need to be conducted as direct and indirect exposure of the soil compartment is unlikely. The substance shows a low adsorptive as well as a bioaccumulative (log Kow = 2.4) potential. Hence, a relevant distribution into soil and a considerable exposure of soil macroorganisms is not expected.*"
Your justification for waiving does not meet the criteria of the specific adaptation rules of Column 2 of Annex IX, Section 9.4. Your argument that there is no direct or indirect exposure is not justified and supported by evidence. ECHA first notes that according to Chapter R.7c of the ECHA *Guidance on information requirements and chemical safety assessment* (version 3.0, June 2017) in case of readily biodegradable substances which are not directly applied to soil it is generally assumed that the substance will not enter the terrestrial environment indirectly via sludge application. However, ECHA notes that direct exposure of the soil cannot be ruled out based on the information provided by you, due to e.g. reported consumer uses as biocidal products (ERC 8a and 8d). Therefore, the adaptation cannot be accepted.

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

Based upon the available aquatic toxicity information and the physico-chemical properties of the substance and in relation to section R.7.11.6., Chapter R.7c of the ECHA *Guidance on information requirements and chemical safety assessment* (version 3.0, June 2017), ECHA considers that the substance would fall into soil hazard category 2. In the context of an integrated testing strategy for soil toxicity, the Guidance advocates performing an initial screening assessment based upon the Equilibrium Partitioning Method (EPM), together with a confirmatory short-term soil toxicity test. The PNECscreen is calculated through EPM on the basis of aquatic toxicity data only.

According to ECHA Guidance on information requirements and chemical safety assessment (version 3.0, June 2017), Chapter R.7C, Section R.7.11.3.1) Earthworm, acute toxicity test (test method: EU C.8./OECD TG 207) and Terrestrial plants, growth test (test method: OECD TG 208 are considered sufficient to fulfil the short-term soil toxicity standard information requirements.

OECD TG guideline 208 (Terrestrial plants, growth test) considers the need to select the number of test species according to relevant regulatory requirements, and the need for a reasonably broad selection of species to account for interspecies sensitivity distribution. For short-term toxicity testing, ECHA considers three species as the minimum to achieve a reasonably broad selection. Testing shall be conducted with species from different families, as a minimum with one monocotyledonous species and two dicotyledonous species, selected according to the criteria indicated in the OECD TG 208 guideline. You should consider if testing on additional species is required to cover the information requirement.

In your comments to the draft decision you indicate that as algae is the most sensitive species in aquatic testing you would perform a confirmatory terrestrial study according to the OECD TG 208. ECHA considers this approach justified.

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: Earthworm, acute toxicity test (test method: EU C.8./OECD TG 207), or, Terrestrial plants, growth test (test method: OECD TG 208), with at least three species tested (with as a minimum one monocotyledonous species and two dicotyledonous species).

12. Effects on soil micro-organisms (Annex IX, Section 9.4.2.)

"Effects on terrestrial organisms" is a standard information requirement as laid down in Annex IX, Section 9.4. of the REACH Regulation. Adequate information on effects on short-term toxicity to invertebrates (Annex IX, Section 9.4.1.), effects on soil micro-organisms (Annex IX, Section 9.4.2.), and short-term toxicity to plants (Annex IX, Section 9.4.3.) needs to be present in the technical dossier for the registered substance to meet the information requirements.

You have waived the standard information requirements of Annex IX, Section 9.4.2 using the following justification: *"In accordance with column 2 of REACH Annex IX, the effects on soil microorganisms study does not need to be conducted as direct and indirect exposure of the soil compartment is unlikely. The substance shows a low adsorptive as well as a bioaccumulative (log Kow = 2.4) potential. Hence, a relevant distribution into soil and a considerable exposure of soil microorganisms is not expected."*

Your justification for waiving does not meet the criteria of the specific adaptation rules of Column 2 of Annex IX, Section 9.4., as explained under request 11 of this decision.

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

ECHA notes that the test requested under point (11) above is not sufficient to address this standard information requirement. ECHA concludes that the effects on soil microorganisms need to be ascertained by performing a relevant test.

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 3.0, June 2017), Chapter R.7C, Section R.7.11.3.1., the nitrogen transformation test is considered sufficient for most non-agrochemicals.

In your comments to the draft decision you agreed to perform the requested test.

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: Soil microorganisms: nitrogen transformation test (test method: EU C.21./OECD TG 216).

Notes for your consideration for terrestrial toxicity (requests 11 and 12)

As the Guidance advocates performing an initial screening assessment based upon the EPM, together with a confirmatory short-term soil toxicity test (the short-term terrestrial toxicity test, specified above), which you are requested to carry out by the present decision, ECHA considers that at this stage it is not possible to determine whether a test will be required to fulfil the remaining standard information requirement in section 9.4. of Annex IX of the REACH Regulation.

Therefore, once results of the requested terrestrial toxicity test are available, you should consider whether there is a need to investigate further the effects on terrestrial organisms in order to fulfil the information requirements of section 9.4 of Annex IX, and if necessary, submit testing proposals for additional terrestrial toxicity tests. If you conclude that no further investigation of effects on terrestrial organisms is required, you should update your technical dossier by clearly stating the reasons for adapting the information requirements of Annex IX, section 9.4. of the REACH Regulation.

ECHA emphasises that the intrinsic properties of soil microbial communities are not addressed through the EPM extrapolation method and therefore the potential adaptation possibility outlined for the information requirement of Annex IX, Section 9.4. does not apply for the present endpoint.

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 9 May 2018.

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

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

ECHA took into account your comments and did not amend the request(s). You requested the possibility to update the registration dossier, which ECHA addressed in a separate communication to you.

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

2. Failure to comply with the 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.