EUROPEAN CHEMICALS AGENCY

Helsinki, 14 December 2018

Addressee: [redacted]

Decision number: CCH-D-2114453634-47-01/F
Substance name: Cinnamyl alcohol
EC number: 203-212-3
CAS number: 104-54-1
Registration number: [redacted]
Submission number: [redacted]
Submission date: 18/12/2017
Registered tonnage band: 10-100

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. **Name or other identifier of the substance (Annex VI, Section 2.1.);**
   - **Chemical name**
   - **EC and/or CAS entry**
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 the study requested under section 2. has negative results;**
4. **and 5. Combined repeated dose toxicity study with the reproduction/developmental toxicity screening study (Annex VIII, Section 8.6.1. and Section 8.7.1.; test method: OECD TG 422) in rats, oral route with the registered substance.**

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

You have to submit the requested information in an updated registration dossier by **3 January 2020**. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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

ECHA
EUROPEAN CHEMICALS AGENCY

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

SUBSTANCE IDENTITY INFORMATION

In accordance with Article 10(a)(ii) of the REACH Regulation, the technical dossier must contain information on the identity of the substance as specified in Annex VI, Section 2 to the REACH Regulation. In accordance with Annex VI, Section 2 the information provided has to be sufficient to enable the identification of the registered substance.

1. Name or other identifier of the substance (Annex VI, Section 2.1.)

Annex VI, section 2 lists information requirements that shall be sufficient to identify the registered substance, including the name or other identifier of the registered substance (Annex VI, 2.1.). More in detail, the information requirements listed in Annex VI, section 2.1. include: a name in the IUPAC nomenclature (section 2.1.1.), EINECS or ELINC'S number (if available and appropriate) (section 2.1.3), CAS name and CAS number (if available) (section 2.1.4).

On the one hand, you have identified the registered substance as a mono-constituent substance using the EINECS number 203-212-3. This entry corresponds to the generic name "Cinnamyl alcohol", which refers to a multi-constituent substance consisting of the two possible isomers of 3-phenylprop-2-en-1-ol (i.e. isomers where the double bound geometry defined as 2E and 2Z). Also, you have used the CAS entry 104-54-1 (2-Propen-1-ol, 3-phenyl-), which is also the generic entry covering the E and Z isomers of 3-phenylprop-2-en-1-ol.

On the other hand, in IUCLID section 1.4, the analytical data (GC and NMR) confirm the mono-constituent identity of the substance. In particular, the GC chromatogram shows one sharp peak with retention time of 4.519 minutes and an area of 99.8 %, and the carbon NMR spectrum shows the presence of one constituent. The analytical data provided is in line with the indications reported in the "Guidance for identification and naming of substances under REACH and CLP" (referred thereafter as the SID Guidance, available on the ECHA website) for the identification of a mono-constituent substance (one main constituent with a concentration >80%).

With a view to the above, ECHA concludes that there is an inconsistency between the identifiers EC 203-212-3 and CAS 104-54-1 (both relative to a multi-constituent substance) on one side, and the analytical data (relative to a mono-constituent substance) on the other side.

Therefore, you are requested to resolve the inconsistency described above by providing the identifiers (chemical name and CAS number) that would correctly identify your substance.

Notes for you consideration

The SID Guidance explains that a mono-constituent substance is:

- a substance, defined by its quantitative composition, in which one main constituent is present to at least 80%;
- identified by the chemical name and other identifiers (including the molecular and structural formula) of the main constituent.

On the contrary, a multi-constituent substance is a substance, defined by its quantitative composition, in which more than one main constituent is present in a concentration ≥ 10% (w/w) and <80% (w/w).

Based on the information given in the dossier (in particular the values of the carbon NMR spectrum), it seems that the registered substance should be regarded as the mono-constituent substance referring to the specific isomer with a E configuration of the double bond (2E)-3-phenylprop-2-en-1-ol. This would correspond to CAS 4407-36-7 (whereas the Z isomer would have CAS 4510-34-3).

If your substance is the multi-constituent substance relative to EC 203-212-3 and CAS 104-54-1, then you shall provide analytical data or other information that would support the identification of the substance as the mixture of the two isomers (2E)-3-phenylprop-2-en-1-ol and (2Z)-3-phenylprop-2-en-1-ol. The analytical data should be provided in section 1.4. In addition, you shall provide the ratio of the isomers, as requested by the REACH regulation according to Annex VI, section 2.2.2. The ratio should be provided in IUCLID section 1.2 (in the composition).

Instead, if your substance is a mono constituent substance, you shall provide the correct chemical name in the "IUPAC name" field and appropriate CAS number in the "CAS information" field in IUCLID section 1.1.

- In case of the E isomer the identifiers would be:
  Chemical name: (2E)-3-phenylprop-2-en-1-ol and CAS entry: 4407-36-7.

- In case of the Z isomer the identifiers would be
  Chemical name: (2Z)-3-phenylprop-2-en-1-ol and CAS entry: 4510-34-3. In this case, relevant analytical data should be provided, because currently, as mentioned above, the provided carbon NMR spectrum seems to correspond to the E isomer.

In both cases, the current CAS 104-54-1 is not appropriate to identify a mono-constituent substance, and should be moved to the "Other identifiers" field. The EC entry 203-212-3 as well cannot be used to identify the mono-constituent substance, but it cannot be removed or modified at this stage, because your registration is linked to this number in REACH-IT. You should instead provide in the 'Remarks' field in IUCLID section 1.1 the following test: "*The currently assigned EC entry 203-212-3 does not specifically correspond to the registered substance since it does not consider a specific geometry of the doubble bonds. This identifier cannot be modified or deleted at this stage in the present registration update for technical reasons.*"

You shall ensure that representative identifiers are used throughout the dossier, and that these identifiers are consistent with the information on the identification of the registered substance in section 1.1, the composition in section 1.2 and the analytical data in section 1.4 of the IUCLID dossier.

You should note that ECHA has established a process, subject to certain conditions, enabling registrants to adapt the EC identifier of an existing registration, while maintaining the regulatory rights already conferred to the substance concerned.

Pending the resolution of the non-compliances addressed in the present decision, any possible adaptation of the identifier can only become effective once ECHA is in a position to establish unambiguously the identity of the substance intended to be covered by you with this registration. Should the information submitted by you as a result of the present decision enable ECHA to identify the substance unambiguously and result in a need to

modify the identifier of the substance, the process of adapting the identifier will be considered relevant. In that case, ECHA will inform you in due time as to when and how the identifier adaptation process shall be initiated.

In any case, you should note that the application of the process of adapting the identifier does not affect your obligation to fulfil the requirements specified in this decision.

In your comments to the draft decision you expressed your intention to:

- *Keep the name of the substance as cinnamyl alcohol;*
- *Include the isomeric names as well into the alternative identify of this substance;*
- *Update the analytical details to keep this name with multi constituent entry.*

ECHA points out that the decision prescribes, above in the present section, the conditions to follow in order to bring your dossier into compliance. These prescriptions depend on your determination of whether the substance is a muticonstituent substance or a monoconstituent substance. ECHA reminds you that the determination of the monoconstituent or multiconstituent nature of the substance must be supported in the dossier by corresponding analytical information obtained on the substance actually manufactured or imported.

TOXICOLOGICAL INFORMATION

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 10 to 100 tonnes per year must contain, as a minimum, the information specified in Annexes VII to VIII 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 under Annex XI, Section 1.5. of the REACH Regulation.

ECHA has considered first the scientific and regulatory validity of your read-across approach in general before assessing the individual endpoints (sections 4. and 5. in the below).

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 endpoints:

- a short-term repeated dose toxicity (28 days) study (Annex VIII, Section 8.6.1.)
- screening for reproductive/developmental toxicity study (Annex VIII, Section 8.7.1.)

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.

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 cinnamyl alcohol (EC no. 203-212-3) using data of structurally similar substances: cinnamaldehyde (EC No. 203-213-9) and α-hexylcinnamaldehyde (EC no. 202-983-3) (hereafter the 'source substances').

ECHA notes that in IUCLID under the *repeated dose toxicity* and *toxicity to reproduction* endpoint summary records you only indicate that both source substances are "*structurally similar*" to the registered substance. However, you have not provided further documentation.

Structural similarity is a prerequisite for applying the grouping and read-across approach. However, structural similarity does not necessarily lead to predictable or similar human health properties. You have not established why a prediction for a human health property is reliable. Thus structural similarity per se is not sufficient to enable the prediction of human health properties of a substance.

On that basis, the requirement of Annex XI, Section 1.5., that human health effects may be predicted from data for reference substance(s) within the group, has not been met.

---

[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.
[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).

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

In your comments on the draft decision you indicated that both the target substance and the source substance cinnamaldehyde (EC No. 203-213-9) "*are structurally similar more than 60% and their mechanistic behaviour is also similar. Thus, are expected to behave in similar pattern related to human health hazard aspect.*" Moreover you also state that these two substances "*have all been shown to be rapidly absorbed from the gut, metabolized, and excreted primarily in the urine and to a minor extent in the faeces.*" You also mention two studies ([redacted] 1990 and [redacted] 1994), which are not available in the active registration dossier, to demonstrate that both substances have similar metabolic pathways. ECHA reminds you that this information needs to be addressed as part of the read-across justification, which is absent in the active registration dossier. Hence, currently the information requirement according to Annex XI, Section 1.5. of the REACH Regulation is not met.

Additionally, according to Annex XI, Section 1.5., there needs to be structural similarity between substances to apply read-across. ECHA considers that the outstanding issues on the identity of the substance explained in section 1 above need to be clarified before any read across adaptation can be considered.

ECHA reminds you that this decision does not take into account any updates submitted after 23 April 2018. However, 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 ECHA had sent the final decision).

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.

a) Information provided

You have sought to adapt this information requirement according to Annex XI, Section 1.2., weight of evidence. Hence, ECHA has evaluated your adaptation with respect to this provision.

You have provided the following justification for the weight of evidence adaptation:

"*it can be concluded that cinnamyl alcohol (CAS No. 104-54-1) was negative at doses up to 1500µg/plate in Ames tests [...] with and without metabolic activation. Further, bacterial gene mutation assay was performed by D. Bickers et al., [...] Cinnamyl alcohol (CAS No. 104-54-1) was non mutagenic at concentrations up to 500–4000µg/plate in E. coli strain WP2 uvrA (trp-) without the metabolic activation. Also, cinnamyl alcohol tested positive in*

two out of three DNA repair tests (rec assays) in Bacillus subtilis M45 (rec-) & H17 (rec+). However, the positive results were observed at doses approaching cytotoxic levels (Adams et al., 2004). In addition, the mouse lymphoma assay was performed by Seifried et.al [...] The substance [...] did not induced mutation in the mouse lymphoma L5178Y cells and hence was considered negative (with and without metabolic activation) in L5178Y TK +/- [...] In a similar study by Seifried et.al [...] cinnamyl alcohol induced mutation in the mouse lymphoma L5178Y cells at a dose concentration of 137-600µg/mL both with and without metabolic activation system and hence was considered positive [...] In a non-guideline study investigating DNA damage and repair, the chemical 33.3µM (4468µg) produced negative results in a sister chromatid exchange assay with Chinese hamster ovary cells without metabolic activation. (Adams et al., 2004)."

"*Based on the above mentioned in vitro studies for target substance and by applying weight of evidence approach, it was observed that a few positive results were obtained for substance cinnmayl alcohol, but for the purpose of classification and chemical safety assessement the substance cinnamyl alcohol (CAS No. 104-54-1) was considered to be non genotoxic as per CLP criteria*."

To support your weight of evidence adaptation for the *in vitro* cytogenicity endpoint, you have provided the following sources of information with the registered substance:

i. Ames test [strains tested: *S. typhimurium* TA100, TA1535, TA98, TA1537, TA1538 and *E. coli* WP2 (Bickers *et al.*, 2005 and Sekizawa *et al.* 1982). No test guideline followed. Non GLP. Reliability score of 2.
ii. Ames test [strain tested: *E. coli* WP2 uvr A] (Bickers *et al.* 2005 and Yoo, 1986). No test guideline followed. Non GLP. Reliability score of 2.
iii. *Bacillus subtilis* recombination assay (Adams *et al.*, 2004 and Bickers *et al.*, 2005). No test guideline followed. Reliability score of 2.
iv. Sister chromatid exchange assay in mammalian cells (Adam *et al.*, 2004). No test guideline followed. Reliability score of 2.
v. Mouse lymphoma assay [strain tested: L5178Y cells] (ACToR, 2011). No test guideline followed. Non GLP. Reliability score of 4.

b) ECHA's evaluation and conclusion of the information provided

An adaptation pursuant to Annex XI, Section 1.2. requires 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 property with respect to the information requirement in question including an adequate and reliable documentation while the information from each single source alone is regarded insufficient to support this notion.

Your weight of evidence adaptation needs to address the specific intrinsic properties of the registered substance with respect to the information requirement of Annex VIII, Section 8.4.2. for an *in vitro* cytogenicity study in mammalian cells. ECHA examined whether the set of information presented addresses the properties of the substance by covering, as a minimum, the most relevant elements investigated in the *in vitro* mammalian chromosome aberration test (test method OECD TG 473) or the *in vitro* mammalian cell micronucleus test (OECD TG 487).

ECHA notes that both the Ames (studies i. and ii.) and the *Bacillus subtilis* recombination assays (study iii.) do not provide information on mammalian cells. Moreover, the Ames studies provide information on gene mutation and not on chromosome aberration.

With reference to the *in vitro* DNA damage and/or repair studies, including the recombinant assays and the sister chromatic exchange assay (studies iii. and iv.), according to ECHA's Guidance document[4] these assays do not provide the information required by Annex VIII, Section 8.4.2., because the *in vitro* DNA damage and repair study provides only an indication of induced damage to DNA (but not direct evidence of mutation) via effects of mitotic recombination and sister chromatid exchange (SCE), respectively.

As regards the the mammalian cell gene mutation study (v.), ECHA notes that for this study record a reliability score of 4 has been assigned, hence this study cannot be taken into consideration for this weight of evidence approach. Additionally, this assay also addresses gene mutation and not chromosome aberration.

As a consequence, studies i. to v., fail to provide information on *in vitro* cytogenicity in mammalian cells. Hence, the studies provided in the technical dossier are not relevant for the assessment of this standard information requirement as per Annex VIII, Section 8.4.2.

On this basis, ECHA considers that the individual lines of evidence you provided are not sufficient on their own to fulfil the information requirement for an *in vitro* cytogenicity endpoint. ECHA considers that these individual lines of evidence taken together and with your justification for the adaptation do not provide sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that the registered substance, has or has not a particular intrinsic property, with respect to the information requirement stated in Annex VIII, Section 8.4.2.

Therefore, the general rules for adaptation laid down in Annex XI, Section 1.2. of the REACH Regulation are not met and your adaptation of the information is rejected.

In the absence of other information on this endpoint in your registration 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).

In your comments on the draft decision you indicated your agreement to conduct the study for OECD TG 473.

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.

[4] ECHA's Guidance Document on Information Requirements and Chemical Safety Assessment, (Chapter R.7a: Endpoint specific guidance (version 6.0, July 2017), p551.

ECHA notes that the registration dossier does not contain appropriate study records for this endpoint. Adequate information *on in vitro* gene mutation in mammalian cells will however need to be present in the technical dossier for the registered substance to meet this information requirement provided that the study requested under section 2. has negative results. ECHA set the deadline for provision of the information to allow for sequential testing.

a) Information provided

You have sought to adapt this information requirement according to Annex XI, Section 1.2., weight of evidence. Hence, ECHA has evaluated your adaptation with respect to this provision.

ECHA notes that for this endpoint you have provided the same justification for the weight of evidence adaptation and the same sources of information with the registered substance, as provided for the *in vitro* cytogenicity/*in vitro* micronucleus endpoint, addressed under Appendix 1, section 2.(a) of the present decision.

b) ECHA's evaluation and conclusion of the information provided

An adaptation pursuant to Annex XI, Section 1.2. requires 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 property with respect to the information requirement in question including an adequate and reliable documentation while the information from each single source alone is regarded insufficient to support this notion.

Your weight of evidence adaptation needs to address the specific intrinsic properties of the registered substance with respect to the information requirement of Annex VIII, Section 8.4.3. for an *in vitro* gene mutation study in mammalian cells. ECHA examined whether the set of information presented addresses the properties of the substance by covering, as a minimum, the most relevant elements investigated in the *in vitro* gene mutation study in mammalian cells (OECD TG 476 or 490).

As already explained above under section 2. of the present decision, ECHA notes that both the Ames (studies i. and ii. in Section 2.) and the *Bacillus subtilis* recombination assays (study iii.) do not provide information on mammalian cells.

With reference to the *in vitro* DNA damage and/or repair studies, including the recombinant assays and the sister chromatic exchange assay (studies iii. and iv. in Section 2.), according to ECHA's Guidance document[5] these assays do not provide the information required by Annex VIII, Section 8.4.3., because the *in vitro* DNA damage and repair study provides only an indication of induced damage to DNA (but not direct evidence of mutation) via effects of mitotic recombination and sister chromatid exchange (SCE), respectively.

As regards the the mammalian cell gene mutation study (v.), ECHA notes that for this study record a reliability score of 4 has been assigned, hence this study cannot be taken into consideration for this weight of evidence approach. Additionally, ECHA notes that Annex XI, section 1.1.2., provides that test data from experiments not carried out according to GLP shall be considered equivalent to data generated in accordance with the relevant test methods referred to in Article 13(3) REACH if the four conditions set out in Annex XI,

[5] ECHA's Guidance Document on Information Requirements and Chemical Safety Assessment, (Chapter R.7a: Endpoint specific guidance (version 6.0, July 2017), p551.

section 1.1.2. are met. More specifically, ECHA notes that study record (v.) fails to provide adequate and reliable documentation (Annex XI, Section 1.1.2.(4)), since there is no data on the method used and on the results obtained. ECHA notes that a robust study summary[6] is required under Article 10(a)(vii). ECHA considers that the information provided in this study record does not meet the requirements of a robust study summary, as defined in Article 3(28). Limited information has been provided hence ECHA cannot fully assess the relevance of the results obtained.

As a consequence, studies i. to v., fail to provide adequate information on *in vitro* gene mutation in mammalian cells. Hence, the studies provided in the technical dossier cannot be used for the assessment of the standard information requirement as per Annex VIII, Section 8.4.3.

ECHA considers that the individual lines of evidence you provided are not sufficient on their own to fulfil the information requirement for an *in vitro* gene mutation endpoint. ECHA considers that these individual lines of evidence taken together and with your justification for the adaptation do not provide sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that the registered substance, has or has not a particular intrinsic property, with respect to the information requirement stated in Annex VIII, Section 8.4.3.

Therefore, the general rules for adaptation laid down in Annex XI, Section 1.2. of the REACH Regulation are not met and your adaptation of the information requirement is rejected.

In your comments on the draft decision you again refer to studies (iii.) to (v.) mentioned under Appendix I, section 2. As already addressed above, these three studies fail to provide adequate information on *in vitro* gene mutation in mammalian cells.

Additionally, in your comments you refer to various *in vivo* micronucleus assays and to an *in vivo* unscheduled DNA synthesis (UDS) assay, not available in the technical dossier, performed with the analogue substance cinnamaldehyde (EC No. 203-213-9). However, ECHA notes that none of these *in vivo* studies are relevant for the assessment of this standard information requirement as per Annex VIII Section 8.4.3. studies because of the following:

(i.) As explained above in Appendix 1, under the *Grouping of substances and read-across approach* section of this decision, the information requirement according to Annex XI, Section 1.5. of the REACH Regulation is currently not met; and

(ii.) The *in vivo* micronucleus studies referred to in your comments do not address gene mutation (but chromosome aberration) while the liver unscheduled DNA synthesis (UDS) assay provides only an indication of induced DNA damage followed by DNA repair (but not direct evidence of mutation). Moreover, according to the ECHA's Guidance[7], a negative result in a UDS assay alone is not a proof that a substance does not induce gene mutation, and so this *in vivo* study does not provide an adaptation for the lack of an *in vitro* gene mutation study.

Finally in your comments you indicate that there are "*other supporting studies which confirms the substance is not genetically toxic substance*". However, ECHA notes that you

[6] ECHA's Practical Guide 3: "*How to report robust study summaries*", (Version 2.0, November 2012), http://echa.europa.eu/documents/10162/13643/pg_report_robust_study_summaries_en.pdf

[7] ECHA Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7a: Endpoint specific guidance, Section R.7.7.6.3, Version 6.0

did not further substantiate this statement by referring to gene mutation studies with the registered substance neither in your comments on the draft decision nor in the technical dossier. Only studies that address gene mutation may enable you to eventually comply with the present information requirement.

In the absence of other information on this endpoint in your registration 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 the study requested under section 2. has negative results.

4. Short-term repeated dose toxicity (28 day), oral route (Annex VIII, Section 8.6.1.)

A "short-term repeated dose toxicity study (28 days)" is a standard information requirement as laid down in Annex VIII, Section 8.6.1. 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.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex VIII, Section 8.6.1., column 2, where the short-term toxicity study (28 days) does not need to be conducted if "*a reliable [...] chronic toxicity study is available, provided that an appropriate species, dosage, solvent and route of administration were used*", by providing the following study records with the registered substance:

i. Key study: chronic toxicity study in rats, oral route (Adams *et al.* 2004). No test guideline followed. Non GLP. Reliability score of 2.
ii. Supporting study: chronic toxicity study in rats, oral route (RTECS database, 2012). No test guideline followed. Non GLP. Reliability score of 4.

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex VIII, Section 8.6.1., column 2 because both chronic studies cannot be considered as being reliable studies due to the noted deficiencies related to the dosage and the sex of species used. More specifically, ECHA notes that in both studies only one dose was tested and only the male species was tested. According to the OECD TG 452 (chronic toxicity studies) "*at least three dose levels and a concurrent control should be used*" and "*at least 20 animals per sex per group should normally be used at each dose level*". The REACH Regulation further requires that both male and female be tested according to Annex 8.6.1. column 1.

Moreover, ECHA notes that non test guidelines and/or non GLP study records should meet the conditions set out in Annex XI Section 1.1.2. With reference to study record (i.) ECHA notes that there is no adequate and reliable documentation hence condition (4) of Annex XI Section 1.1.2. is not met and as a consequnce the data cannot be considered to be equivalent to the data generated by the corresponding test method referred to in Article 13(3). More specifically, in the specific study record there is no information specified on

clinical observations, body weight, food consumption and compound intake, food efficiency, water consumption and compound intake, opthalmoscopic examination, urinalysis, neurobehavioral examination, immunology, and histopatholgical examinations. There is also no information on the results obtained for the parameters that were indicated as being performed, such as clinical chemistry and haematology. In addition ECHA considers that the information provided in this study record does not meet the requirements of a robust study summary, as defined in Article 3(28). As regards the secondary source data from RTECS database (study ii.), with an assigned reliability score of 4, ECHA notes that this information cannot be taken into consideration for the assessment of this endpoint.

In the technical dossier you further provided two sub-chronic repeated dose toxicity (90-day) study records (no test guideline followed / non GLP / reliability score of 2) with the analogue substance cinnamaldehyde (EC No. 203-213-9). However, as explained above in Appendix 1, under the *Grouping of substances and read-across approach* section of this decision, the information requirement according to Annex XI, Section 1.5. of the REACH Regulation is not met.

In your comments on the draft decision you again refer to studies (i.) and (ii.), referred to under this section. However, these two studies with the registered substance, as explained above, fail to provide adequate information on the short-term repeated dose toxicity endpoint. You again also refer to two sub-chronic repeated dose toxicity (90-day) study records performed with the analogue substance cinnamaldehyde (EC No. 203-213-9). However, as explained above in Appendix 1, under the *Grouping of substances and read-across approach* section of this decision, currently the information requirement according to Annex XI, Section 1.5. of the REACH Regulation is not met.

As currently none of the information provided in your registration dossier meets the REACH standards for adapting the standard information there is an information gap in your dossier and it is necessary to provide information for this endpoint.

When there is no information available for the 28-day repeated dose toxicity endpoint (EU B.7, OECD TG 407) and the screening study for reproductive/developmental toxicity (OECD TG 422 as explained below under point 5.), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is requested to ensure that unnecessary animal testing is avoided. Such an approach offers the possibility to avoid carrying out a 28-day study according to OECD TG 407, because the OECD TG 422 can at the same time fulfil the information requirement of REACH Annex VIII, 8.6.1 and that of REACH Annex VIII, 8.7.1.[8].

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, even though the information indicates that human exposure to the registered substance by the inhalation route is likely, potential inhalation-specific effects are already addressed by deriving a long-term DNEL for inhalation, local effects. Hence, the test shall be performed by the oral route using the test method OECD TG 422.

According to the test method OECD TG 422 the rat is the preferred species. ECHA considers

[8] ECHA's Guidance Document on Information Requirements and Chemical Safety Assessment, Chapter R.7a: Endpoint specific guidance, Section R.7.6.2.3.2., p. 484 to 485 (version 6.0, July 2017).

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

5. 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.

a) Information provided

You have sought to adapt this information requirement according to Annex XI, Section 1.2., weight of evidence. Hence, ECHA has evaluated your adaptation with respect to this provision.

For your weight of evidence adaptation you have provided the following sources of information:

i. QSAR prediction with the registered substance using OECD QSAR toolbox version 3.3 (SSS, 2017). Reliability score of 2.
ii. Short-term *in vivo* reproductive toxicity assay (Hardin *et al.*, 1987) with the analogue substance cinnamaldehyde (EC No. 203-213-9). No test guideline followed. Non GLP. Reliability score of 2.
iii. One-generation reproductive toxicity study conducted similarly to OECD TG 421 with the analogue substance α-hexylcinnamaldehyde (EC no. 202-983-3). Secondary source: published in a NICNAS study report in 2017. Reliability score of 4.

You have provided the following weight of evidence adaptation with respect to reproductive toxicity: On the basis of the studies indicated above, you conclude that the "*target substance and read across substance by applying weight of evidence approach and also according to CLP criteria, it can be concluded that no adverse effects on sexual function and fertility was observed i.e chemical is not expected to cause reproductive toxicity and hence the substance Cinnamyl alcohol (CAS No. 104-54-1) cannot be classified as reproductive toxicant.*"
ECHA notes that since as part of the weight of evidence approach you provided a QSAR prediction (study i.) ECHA has also evaluated this study with respect to provision Annex XI, Section 1.3.

Moroever, since studies (ii.) and (iii.) are non test guidelines and/or non GLP study records, ECHA has evaluated these studies with respect to provision Annex XI, Section 1.1.2.

b) ECHA's evaluation and conclusion of the information provided

An adaptation pursuant to Annex XI, Section 1.2. requires 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 property with respect to the information requirement in question including an adequate and reliable documentation while the information from each single source alone is regarded insufficient to support this notion.

Your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance with respect to a screening study (OECD TG 421/422). Relevant elements are in particular exposure route, duration and levels, investigations of the effects on male and female reproductive performance, histopathological information on reproductive organs, initial information on the offspring and additional parameters for endocrine disrupting modes of action.

ECHA notes that as part of the weight of evidence approach you sought to cover the information requirement on reproductive toxicity by means of a read-across based on a category approach supported by the QSAR Toolbox. However, ECHA notes that the QSAR prediction is not valid and its use is not adequate for the regulatory purpose.

More specifically, you failed to provide a read-across hypothesis including an assessment supported by scientific justifications of the impact of the structural differences between the source and the target substances on the properties of these substances. The report attached to the endpoint study record only contains the automatically generated report from the (Q)SAR Toolbox. No further information was added to justify the prediction in the editable fields available in the Toolbox report (e.g. category hypothesis) or in the endpoint study record. The following elements are missing:

- Justification why the analogues identified by the Toolbox are considered adequate for a read-across prediction: ECHA notes that the analogue substances used for the read-across prediction are not adequate due to lack in chemical similarity and insufficient information on mode of action.Justification why an average value from the NOAEL of the five closest analogues identified by the Toolbox is an appropriate way to estimate the NOAEL of the target substance.
- Considerations on the data quality for the source studies.

Hence, ECHA considers that the category hypothesis is not substantiated, and consequently you have not provided a reliable basis whereby the properties of the registered substance may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group. Additionally, ECHA notes that the data used for the read-across calculation are a mix of different parameters, different test guidelines (OECD TGs 408, 409, 422 and others), different routes of exposure (dermal/oral), different units (nominal and actual dosing), etc, which makes it impossible to derive a scientifically robust value.

As a consequence the conditions set in Annex XI Section 1.3 ((Q)SAR) are not met. Hence, these QSAR results cannot be used instead of testing. As a consequence, ECHA considers this data, as currently provided, does not constitute relevant and reliable information in the context of this weight of evidence approach.

With reference to studies ii. and iii. performed with the analogue substances, since the read-across approach for these studies is rejected (see Appendix 1, under the *Grouping of substances and read-across approach* section above) this information currently cannot be used as reliable source of information within a weight of evidence adaptation.

Moreover, ECHA notes the following shortcomings in studies (ii.) and (iii.):

i. In study (ii.) only females were exposed, there was a short exposure duration (gestation days 6-13) and only one dose was tested. ECHA notes that the screening study uses male and female rats dosed with the test substance for two weeks prior to mating, during mating and gestation (three weeks), and parturition up until postnatal day 13. In addition, at least three dose levels plus control should be used and each group should have at least ten mating pairs. Consequently, the study fails to meet the second and third conditions set out in Annex XI, Section 1.1.2. (2) and (3) since it does not provide adequate and reliable coverage of key parameters, including a comparable exposure duration, as foreseen to be investigated in OECD test guideline 421/422.

ii. You assigned a reliability score of 4 (not assignable) to study iii. In view of the reliability you assigned, additionally, this secondary source information cannot be used as a reliable source of information within your weight of evidence adaptation.

Hence, the sources of information you provided, together with your justification for the adaptation, do not allow to assume/conclude on the intrinsic property of the registered substance with respect to the information requirement for Annex VIII, Section 8.7.1.

Therefore, the general rules for adaptation laid down in Annex XI, Section 1.2. of the REACH Regulation are not met and your adaptation of the information requirement is rejected.

Finally, ECHA notes that a pre-natal developmental toxicity study with the registered substance (Bickers *et al.*, 2005) is also available in the technical dossier. The study does not follow any test guidelines, is non GLP complaint and has been assigned a reliability score of 2. ECHA notes the following deficiencies in the study by Bickers *et al.* (2005):

i. The study does not provide adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test method OECD TG 414 (Annex XI, Section 1.1.2. (2)). This is because in the study (i.) only two doses were tested' amd (ii.) only 14 to 15 female rats were tested. According to OECD TG 414 at least (i.) 3 dose levels should be tested; and (ii.) 20 pregnant females per group should be used.

ii. The exposure duration is shorter than the corresponding test method (OECD TG 414) (Annex XI, Section 1.1.2 (3)). In this study it seems that the test species were only exposed during their pregnancy, hence the test species was not exposed from preimplantation or at least from implantation, as indicated in OECD TG 414.

iii. There is information missing on the study design and on maternal and fetuses examinations, hence no adequate and reliable documentation was provided (Annex XI, Section 1.1.2. (4)).

In view of the noted deficiencies above, the study fails to meet the second, third and fourth conditions set out in Annex XI, Section 1.1.2. Hence, the pre-natal developmental study record provided in the technical dossier is incompliant in respect of the information requirement of Annex IX, 8.7.2 (pre-natal developmental toxicity). As a consequence, the study cannot be used to adapt the information requirement of Annex VIII, 8.7.1, according to column 2 (i.e. that a pre-natal developmental toxicity study is available).

In your comments on the draft decision you indicated your intention to update the technical dossier with "*full study publications*" of two studies addressing embryotoxic effects of the registered substance. ECHA reminds you that this decision does not take into account any updates submitted after 23 April 2018.

Nevertheless, we can already provide the following comments based on the information you provided to us. ECHA can already point out that both studies fail to meet the second and third conditions set out in Annex XI, Section 1.1.2. (2) and (3) since they do not provide adequate and reliable coverage of key parameters, including a comparable exposure duration, as foreseen to be investigated in OECD test guideline 421/422. In both studies only females were exposed, throughout gestation period only (shorter exposure duration) and only one dose was tested. ECHA notes that the screening study uses both male and female rats and the female rats need to be dosed with the test substance two weeks prior to mating, (up to) 14 days mating, 22 days gestation and 13 days lactation. In addition, at least three dose levels plus control should be used and each group should have at least ten mating pairs. These are critical deficiencies that would disqualify this information for bringing the dossier into compliance.

Finally, in your comments on the draft decision you also indicate that you intend to conduct a pre-natal developmental toxicity study with an analogue substance [cinnamaldehyde (EC No. 203-213-9)]. ECHA notes that a study on this analogue substance has been requested in a separate compliance check decision (communication number CCH-D-2114436058-50-01/F). Moreover, you state that you will use this study to waive the screening study with the registered substance. ECHA notes that indeed according to Annex VIII Section 8.7.1., the screening for reproductive/developmental toxicity study (OECD TG 421 or 422) does not need to be conducted if "*a pre-natal developmental toxicity study (Annex IX, 8.7.2) [...] is available*." However, currently in the technical dossier there is no compliant study available that can be used to adapt this information requirement according to Annex VIII Section 8.7.1, column 2, and as explained above in Appendix 1, under the *Grouping of substances and read-across approach* section of this decision, the information requirement according to Annex XI, Section 1.5. of the REACH Regulation is currently not met.

Hence, 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.

When a screening study for reproductive/developmental toxicity (OECD TG 422) and a 28-day study (EU B.7, OECD TG 407, see point 4. above) is not available, the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is requested to ensure that unnecessary animal testing is avoided. This approach offers the possibility to avoid carrying out a 28-day study, because the OECD TG 422 can at the same time fulfil the information requirement of REACH Annex VIII, 8.7.1 and that of REACH Annex VIII, 8.6.1. According to the test methods OECD TG 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 crystalline solid, 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:
- Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

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.

An informal call with you was held on 26 October 2017, giving you the opportunity to revise substance identity issues. During the call you agreed to update your dossier addressing the substance identity issues by 22 December 2017. The dossier was updated on the 18 December 2017, however the substance identity issues were not addressed.

The compliance check was initiated on 30 January 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 requests.

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.