ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 17 May 2018

Addressee: [redacted]

Decision number: CCH-D-2114407681-54-01/F
Substance name: Piperonal
EC number: 204-409-7
CAS number: 120-57-0
Registration number: [redacted]
Submission number: [redacted]
Submission date: 23/05/2017
Registered tonnage band: 10-100 (Joint submission tonnage band: 100-1000 tpa)

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. **Composition of the substance (Annex VI, Section 2.3.);**
   - **Identification and quantification of the impurities, as specified in Appendix 1, section 1;**
2. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD 421 or 422) in rats, oral route with the registered substance;**
3. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats with the registered substance;**
4. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

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

You have to submit the requested information in an updated registration dossier by **24 November 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.

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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 **Claudio Carlon**, Head of Unit, Evaluation **E2**

[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

1. Composition of the substance (Annex VI, Section 2.3.)

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.

Annex VI, section 2.3. of the REACH Regulation requires that each registration dossier contains sufficient information for establishing the composition of the substance as registered by its legal entity. In that respect, according to chapter 4.2 of the Guidance for identification and naming of substances under REACH and CLP (Version: 2.1, May 2017) – referred to as the "SID Guidance", you shall note that, for well-defined substances, the following applies:

- Each main constituent (i.e. the constituent present at ≥80% for mono-constituent substance or each constituent present at ≥10% and < 80% for multi-constituent substance) shall be identified and reported individually; and
- Each impurity present at ≥1% or relevant for the classification and/or PBT assessment of the registered substance shall be identified and reported individually.
- For each constituent, the typical, minimum and maximum concentration levels shall be specified regardless of the substance type.

In the present dossier you have identified the registered substance as a well-defined mono-constituent substance and in IUCLID section 1.2 you have reported the main constituent "piperonal" with a degree of purity and a concentration range of 80-100% (typical concentration >[redacted]%). In addition, you have reported unknown impurities with a concentration range of 0.0-20.0% (typical concentration ≥[redacted]%). The chromatographic results provided in section 1.4, shows a main peak with the rel. area [%] of [redacted]% and some additional three small peaks with rel. area of [%] of <<1% each. None of the peaks were labelled, but it is understandable that the main peak is relative to "piperonal" (the main constituent), whereas the other peaks are relative to the impurities.

ECHA notes that up to 20% of the composition, being impurities as reported in section 1.2 has not been identified and quantified. In addition, it is indicated in the dossier that the typical concentration of unknown impurities is ≥[redacted]% and at the same time the typical concentration of the main constituent is reported as >[redacted]%. This typical concentrations are not consistent with each other. Although, the provided analytical data in section 1.4 indicates that impurities are present only at a low level, based on the reported composition in section 1.2 the absence of impurities at ≥1% or relevant for classification and/or PBT assessment (that shall be reported as part of the composition) cannot be excluded.

In case the impurities are present at a concentration >1% or are relevant for classification and/or PBT assessment, these impurities must be identified and reported in section 1.2, as explained in the SID guidance. Consequently, you will need to provide a complete compositional information of all the relevant impurities as described above and report their typical, minimum and maximum concentration levels.

If the concentration ranges provided in the current dossier do not reflect the composition

profile of the substance as imported and/or manufactured they should be revised in a way that they reflect your legal entity composition as manufactured and/or imported.

The requested information shall be included in section 1.2 of the IUCLID dossier. You shall ensure that the composition is verifiable and therefore supported by a description of the analytical methods for the identification and quantification of the constituents required to be reported, as required under Annex VI 2.3.7. of the REACH Regulation. The compositional information of the substance should be completed up to 100%.

In your comments on the draft decision you confirmed that the composition of the substance will be updated and aligned according to Chapter 4.2 of the Guidance for identification and naming of substances under REACH and CLP (Version: 2.1, May 2017) – referred to as the "SID Guidance".

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

ECHA notes that the tonnage band for two members of the joint submission is 100 to 1 000 tonnes per year. 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.

"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.

You did not provide any justification on the weight of evidence adaptation on how the sources of information/studies, which you have provided enable an assumption or conclusion that the registered substance does or does not have a dangerous property with respect to reproductive toxicity.

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

i. "*An evaluation of food flavoring ingredients using an in vivo reproductive and developmental toxicity screening test*" (Vollmuth *et al.*, 1990) according to OECD TG 421 with the registered substance, Klimisch reliability 2; and
ii. "*Detection of chemical mutagens by the dominant lethal assay in the mouse*" (Epstein *et al.*, 1972) according to OECD TG 478 with the registered substance, Klimisch reliability 2.

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

Evaluation approach/criteria

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.

Evaluation of the provided information

In the technical dossier, under this endpoint, you have provided a "*reproductive and developmental toxicity screening test*" (study i. above).

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 conditions set out in Annex XI , section 1.1.2. are met.

ECHA notes that the above study is a non-GLP study and so must meet the requirements of Annex XI, Section 1.1.2. Contrary to that provision, there are a number of shortcomings identified in this study arising from adequate and reliable coverage of key parameters, study duration and adequate and reliable documentation:

- Missing information on the test substance, housing conditions, and on the positive control,
- Missing data on the organ weight and histopathology of reproductive organs (OECD TG 421/422 provides that for male fertility assessment "*a detailed histological examination of the testes is essential.*"),
- Shorter exposure time ("*7 days prior to cohabitation, during the cohabitation period (up to 7 days), during gestation, and up to 4 days post-partum"* versus at least 14 days premating, (up to) 14 days mating, 22 days gestation, 13 days lactation in OECD TG 421/422) with no exposure for males (in OECD TG 421/422 also males are exposed for a minimum of two weeks prior to mating, during the mating period and, approximately, two weeks post-mating),
- Lower number of females (10 instead of "at least 12-13 females"),
- No evaluation of the oestrous cycles,
- No clinical chemistry.

This study fails to meet the requirements of Annex XI, 1.1.2 and hence does not provide adequate information for the information requirement.

As regards study (ii.), that is a rodent dominant lethal assay, ECHA notes that this study does not cover the information required under this endpoint since the dominant lethal assay is used to investigate whether chemicals produce mutations resulting from chromosomal

aberrations in germ cells and to a certain extent genotoxicity. In the dominant lethal assay only males are exposed to the test substance while in the screening study both males and females are treated with the substance. Study (ii.) does not provide the required information on the key elements of a screening study, that is initial information of the effects on male and female reproductive performance (such as gonadal function, mating behaviour, conception and parturition and histopathological information on reproductive organs) and on the offspring (such as mortality, abnormal behaviour and body weight of pups after birth; and additional parameters for endocrine disrupting modes of action). Moreover, due to its limitations the dominant lethal assay is not intended for use as a primary method, but rather as a supplemental test method which can only be used when there is no alternative for regulatory requirements.

Conclusion

You have not provided a weight of evidence justification and so you have failed to provide adequate and reliable documentation of your Weight of Evidence adaptation. The individual studies by themselves fail to meet the information requirement and ECHA considers that there is no basis whereby the information in each individual study can be used to complement the defects in the other study, and hence there is not a sufficient weight of evidence leading to the assumption/conclusion that the substance has or has not a particular dangerous property according to the conditions of Annex XI, 1.2. Hence, the sources of information you provided, do not allow to assume/conclude on the dangerous (hazardous) property of the registered substance with respect to the information requirement for Annex VIII, Section 8.6.1.

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.

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

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

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

In your comments on the draft decision you indicated that you may adapt the screening study according to Annex VIII, Section 8.7.1., column 2, since you intend to perform the

pre-natal developmental toxicity study. ECHA notes that 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.*" ECHA-S also notes the Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7a: Endpoint specific guidance (Version 6.0 July 2017), which states in R.7.6.2.1 "It is strongly recommended that the registrant considers conducting a screening study in addition to the prenatal developmental toxicity study to cover the fertility and early peri/post natal development if an extended one-generation reproductive toxicity study is not conducted."

Notes for your considerations

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

You should also carefully consider the order of testing especially the requested screening (OECD TG 421 or TG 422) and the pre-natal developmental toxicity study (OECD TG 414) to ensure unnecessary animal testing is avoided, paying particular attention to ECHA's *Guidance on information requirements and chemical safety assessment*, Chapter R.7a, Section R.7.5 and 7.6 (version 6.0, July 2017).

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

ECHA notes that the tonnage band for two members of the joint submission is 100 to 1 000 tonnes per year. 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.

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.

In the technical dossier you have provided the following study records with the registered substance:

i. Key study: Sub-chronic (90-day) toxicity study referred to in the following publication: "*Food Flavourings and Compounds of Related Structure. II. Subacute and Chronic Toxicity*" (Hagan *et al.*, 1967). Equivalent to OECD TG 408. Non GLP compliant, Klimisch reliability 2.
ii. Supporting study: Same study referred to under study (i.) in another publication: "*Toxic properties of compounds related to safrole*" (Hagan *et al.*, 1965). Rel. 3.
iii. Supporting study: "[redacted]" Unpublished communication to the [redacted] (1954). Non GLP compliant, Klimisch reliability 3.
iv. Supporting study: Chronic / Carcinogenicity study referred to in the following publication: "*Where we stand concerning the evaluation of flavoring substances from the viewpoint of health.*" (Bar and Griepentrog, 1967). Equivalent to OECD TG 453. Non GLP compliant, Klimisch reliability 2.

v. Supporting study: Sub-chronic (90-day) toxicity study referred to in the following study report: "[redacted]" ([redacted] 1958). Equivalent to OECD TG 408. Non GLP compliant, Klimisch reliability 2.

ECHA notes that all the studies provided (i. to v.) in the technical dossier are considered "*equivalent*" to the test guidelines (with deviations) and are not according to GLP. 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 conditions set out in Annex XI , section 1.1.2. are met. The second condition of Annex XI, 1.1.2. requires that there are adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3) REACH. The fourth condition requires adequate and reliable documentation of the studies provided.

The study referred to in the publications by Hagan *et al*. (1967), (i.) and (ii.) above, fails to provide adequate and reliable documentation and reliable coverage of the key parameters foreseen to be investigated in OECD TG 408, namely:

- Only two doses were tested; according to the OECD TG 408 "*At least three dose levels and a concurrent control shall be used, except where a limit test is conducted*". ECHA notes that no limit test has been conducted, hence the use of only two doses is not justified;
- Only five animals per sex per dose group where tested; according to the OECD TG 408 at least 10 males and 10 females per group should be tested at each dose level;
- The histopathological examination was only performed on 6 or 8 rats and there is no information provided on which tissues were examined; according to the OECD TG 408 "*Full histopathology should be carried out on the preserved organs and tissues of all animals in the control and high dose groups*";
- No clinical chemistry, no urinalysis, no functional battery and
- Very limited information reported in the study record.

Hence the study fails to meet the adaptation as set out in Annex XI, Section 1.1.2., since conditions (2) and (4) are not met.

As regards study record (iii.) ECHA notes that you assigned a reliability score of 3 (not reliable). In view of the reliability you assigned, this information cannot be used as reliable source of information since as you reported the study has "*significant methodological deficiencies*".

With reference to study record (iv.) ECHA notes that this study fails to provide adequate and reliable coverage of the key parameters foreseen to be investigated in OECD TG 408, mainly because the histopathological evaluation was only conducted only on "*liver, kidneys, suprarenal glands, heart, spleen, pancreas, cerebellum, and any identified tumours*", versus about 30 tissues specified by OECD TG 408. Important tissues such as reproductive organs, thyroid, thymus, lymph nodes etc. were not examined. Additionally, haematology, clinical chemistry and urinalysis parameters were not evaluated. Hence the study fails to meet the adaptation as set out in Annex XI, Section 1.1.2., since condition (2) is not met.

Finally, as regards study record (v.), ECHA notes that the study record does not provide the information required by Annex IX, Section 8.6.2., because the study has not been performed with the registered substance but with a mixture containing the registered

substance (~15% of the total mixture). ECHA notes that the high dose tested in this study consisted the equivalent of only 17 mg/kg body weight/day of the registered substance.

Moreover, the study fails to provide adequate and reliable coverage of the key parameters foreseen to be investigated in OECD TG 408, since only two doses were tested, no histopathological examination was performed and no organ weights were recorded (except for liver and kidney). Hence the study also fails to meet the adaptation as set out in Annex XI, Section 1.1.2., since condition (2) is not met.

In your comments on the draft decision you have agreed with ECHA that the individual study records provided cannot be considered to be equivalent to the data generated by the corresponding test methods referred to in Article 13(3) (Article XI, Section 1.1.2.). Hence, you propose to adapt the information requirement according to Annex XI, Section 1.2., weight of evidence. You provided the following justification for the adaptation: "*all the key parameters are covered using the following studies: (1) Hagan et al., 1967 (2) Bar and Griepentrog, 1967*" with the registered substance, and another two additional studies: "*OECD 422, GLP-compliant (2016)*" and "*OECD 411, GLP-compliant (2005)*", with the analogue substance α-Methyl-3,4-methylene-dioxyhydrocinnamic aldehyde (MMDHCA) (EC no 214- 881-6).

Evaluation approach/criteria

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 sub-chronic toxicity study (EU B.26/OECD TG 408). Relevant elements are in particular exposure route, duration and levels, two genders, sensitivity and depth of investigations to detect specific organ toxicity.

Evaluation of the provided information

ECHA notes that the deficiencies of the two studies with the registered substance (studies i. and iv.) have already been pointed out in this section. More specifically, these two studies do not assess some of the key parameters that are required to be evaluated under an OECD TG 408 study.
In your comments you also refer to two other studies (OECD TG 422 and OECD TG 411) that have been performed with the analogue substance α-Methyl-3,4-methylene-dioxyhydrocinnamic aldehyde (MMDHCA) (EC no 214- 881-6).

ECHA notes that you are proposing the same read-across approach that you used for the pre-natal developmental toxicity endpoint. However, in your comments you explain that the read-across approach used for the pre-natal developmental toxicity study is "*no longer required to be valid for developmental toxicity*", however the read-across approach shall be used to justify the read-across approach (for the repeated-dose toxicity endpoint) to the "*OECD TG 422 and OECD TG 411 study data that are available on the Source substance*".

You indicate that the "*read-across is valid*" and is the "*worst-case from a toxicological point of view*". As a support to the read-across hypothesis (referred to under section 4 of this decision) in your comments you refer to two QSAR predictions: (a.) results from "*Bioaccumulation – metabolism half-lives*" profilers from QSAR Toolbox, and (b.) predicted metabolic routes for target and source substances using TIMES in vivo rat liver metabolism model.

With reference to the read-across approach, ECHA notes that you failed to provide clarification/information concerning the arguments raised under section 4 of this decision. More specifically, there are still pending issues concerning the structural differences between the source and target substances, the limited toxicokinetics data and the limited data to allow toxicological comparison between the two substances. Hence, the arguments under section 4 of the decision still hold. ECHA notes that in your comments you agree to perform the sub-chronic toxicity (90-day) study if the read-across approach is not accepted.

As regards the QSAR data, ECHA notes that the information from (a.) should only be used in a qualitative manner, as the Toolbox results are meant to support category formation and they are not recommended to be used directly for prediction purposes (as SARs). Additionally, this information is a prediction of the biotransformation of the substances in fish, hence this may differ from the biotransformation pathways occurring in mammals. With reference to (b.) above, ECHA notes that this information supports your theoretical explanation given on the likelihood of a similar metabolic path for the two molecules. However, ECHA notes that both metabolic pathways predicted by TIMES for the target and the source substance are indicated as out of domain by the software, due to the presence of unknown structural fragments (33% for the target and 22% for the source). Domain check by TIMES software is very strict. Results of this type can be considered of moderate reliability even if flagged as "out of domain" by the software. Furthermore, it was noted that for the target substance, you did not mention one additional predicted primary metabolite that was detected, that is the alcohol (as a result of reduction of the aldehyde functionality, with a probability of formation of 44%). Moreover, ECHA notes that this metabolite (the alcohol) of the target substance is predicted to undergo conjugation at the second step, however, this pathway is not predicted for the source substance. Hence, you cannot conclude that "*the QSAR model TIMES v2.28.1.6 (in vivo rat liver metabolism v07.11) predicts identical metabolic routes for the Source and Target substances*".

With reference to the study records with the analogue substance, ECHA notes that you only provided a "*key parameter comparison*" excel sheet with the main parameters tested in these two studies however, no study reports were provided. ECHA reminds you that this decision does not take into account any updates submitted after 9 November 2017. All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation (after ECHA had sent the final decision).

ECHA can already point out that the screening study (OECD TG 422) with the source substance does not fulfill the standard information requirement of Annex IX Section 8.6.2. The OECD TG 422 study has a shorter exposure duration than the sub-chronic toxicity (90-day) study. As regards the dermal sub-chronic toxicity study ECHA notes that some of the organ weights required to be tested (as per OECD TG 408), such as spleen and thymus, are missing. As already mentioned, the study reports of these two studies are missing. Hence, ECHA is unable to fully evaluate these studies at this stage. Moreover, ECHA notes that

there is also a failure to provide adequate and reliable documentation of the read-across.

Considering the above, ECHA notes that the read-across approach is still considered to be unacceptable, hence this information from OECD TG 422 and OECD TG 411 studies, currently, cannot be used as a reliable source of information within a weight of evidence adaptation.

Conclusion

In the light of the shortcomings presented above ECHA considers that the two studies with the registered susbtance alone are not sufficient to fulfil the information requirement for a sub-chronic toxicity (90-day) study.

Hence, the sources of information you provided, together with your justification for the adaptation, do not allow to assume/conclude that the substance does not have a particular dangerous (hazardous) property with respect to the information requirement for Annex IX, Section 8.6.2.

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

ECHA 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 solid (crystals) however it exists as a liquid at physiologically relevant temperatures. The substance is a water soluble powder with a low vapour pressure (2 Pa). The median particle size is 272 µm, hence the particles are not of an inhalable size (MMAD < 50 µm). Uses with industrial / professional / consumer spray applications are reported in the chemical safety report. However, the reported concentrations are low (<1%). Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408. According to the test method EU B.26./OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats.

Notes for your consideration

ECHA notes that a revised version of OECD TG 408 may be adopted later on this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. After the adoption of the revised version of the OECD TG 408 you should test in accordance with that version of the guideline as published on the OECD website for adopted

test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).
Even if you start testing before the guideline is published, it is appropriate to consider including these endocrine-sensitive parameters in your testing protocol in accordance with the proposed revised version of the draft guideline (see http://www.oecd.org/env/ehs/testing/section4-health-effects.htm).

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

ECHA notes that the tonnage band for two members of the joint submission is 100 to 1 000 tonnes per year. 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.

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

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for an "[redacted]" (publication) (OECD TG 414) with the analogue substance α-Methyl-3,4-methylene-dioxyhydrocinnamic aldehyde (MMDHCA) (EC no 214- 881-6).

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 Piperonal (EC no 204-409-7) using data of a structurally similar substance α-Methyl-3,4-methylene-dioxyhydrocinnamic aldehyde (MMDHCA) (EC no 214-881-6). (hereafter the 'source substance').

You have provided a read-across documentation in the endpoint summary.

You use the following arguments to support the prediction of properties of the registered substance from data for source substances within the group: on the basis of "*structural and physicochemical similarities*", "*as well as the common toxicokinetic and toxicological profiles*". As an integral part of this prediction, you propose that the source and registered substance(s) have similar properties for the above-mentioned information requirements. ECHA considers that this information is your read-across hypothesis.

ECHA's evaluation and conclusion

Your proposed adaptation argument is that the similarity in chemical structure and in some of the physico-chemical, toxicological properties between the source and registered substance is a sufficient basis for predicting the properties of the registered substance for other endpoints. Structural similarity is a prerequisite for applying the grouping and read-across approach. However similarity in chemical structure, and in some of the physico-chemical and toxicological properties does not necessarily lead to predictable or similar human health properties in other endpoints.

[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).

Your justification based on structural similarity, similar physico-chemical, toxicokinetics and toxicological properties has not established why the prediction is reliable for the developmental toxicity endpoint for which the read across is claimed.

Moreover, ECHA notes that you failed to provide an explanation on whether the structural differences noted for the two structures might influence the reactivity of the two substances. The target substance is an aromatic aldehyde while the source substance has an aliphatic chain between the aldehyde and aromatic groups, meaning that it is an aliphatic aldehyde. This difference, though mentioned in the justification document, was not addressed in terms of potentially different toxicity profiles.

You have argued that there are common toxicokinetic profiles for the source and target substance. With reference to in vivo toxicokinetics data, there is only information on the target substance, and hence there is limited data to allow a comparison between the source and the target substance. Therefore it is not possible to draw a reliable conclusion that there is a common toxicokinetic profile, and so this is not a reliable basis for predicting the toxicological properties of the registered substance.

Under any circumstances, toxicokinetic behaviour does not provide a basis for predicting the toxicodynamic behaviour of a substance. As there is not a reliable basis for predicting the toxicodynamic behaviour of the registered substance, the argument of toxicokinetic similarity by itself cannot provide a reliable basis for predicting the toxicological properties of the registered substance.

Finally, as regards the toxicological profile, ECHA notes that for the higher tier endpoints (Sub-chronic toxicity study (90-day), Pre-natal developmental toxicity study, Extended One-Generation Reproductive Toxicity Study) there is limited data to allow a comparison between the two substances. Specifically, the data provided with the target substance for the repeated dose toxicity and reproductive toxicity endpoints were not adequate to cover the data requirements for these endpoints, and on this basis there is not a valid comparison for these endpoints. Additionally, the studies on the source substance for the sub-chronic toxicity endpoint and the fertility endpoint are not provided as endpoint study records, and ECHA is unable to evaluate these studies, nor to make a comparison based on those studies. There is therefore a failure to provide adequate and reliable documentation of the read-across. In view of these shortcomings in the comparison of the toxicological profile, there is not a sufficient basis to conclude on the similarity of the source and target substances. This is an additional reason why it is not possible to predict the toxicity of the target substance on the basis of similar toxicological profile.

Additionally, ECHA has taken into account all of your arguments together. ECHA firstly notes that you have not provided a reasoning as to why these arguments add to one another to provide sufficient basis for read-across. Secondly, the defects of each individual argument are not mitigated by the other arguments you have provided, and so ECHA considers that the arguments when taken all together do not provide a reliable basis for predicting the properties of the registered substance.

Therefore, ECHA considers that this grouping and read-across approach does not provide a reliable basis whereby the human health effects of the registered substance may be predicted from data for reference substance(s) within the group. Hence, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the

REACH Regulation.

As described above, further elements are needed to establish a reliable prediction for a toxicological 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.

Therefore, your adaptation of the information requirement is rejected.

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

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a soluble 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: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a first species (rat or rabbit) by the oral route.

ECHA notes that in your comments on the draft decision you indicated your intention to perform the requested study with the registered substance.

Notes for your consideration

ECHA notes that a revised version of OECD TG 414 may be adopted later on this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. After the adoption of the revised version of the OECD TG 408 you should test in accordance with that version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788.

Even if you start testing before the guideline is published, it is appropriate to consider including these endocrine-sensitive parameters in your testing protocol in accordance with the proposed revised version of the draft guideline (see http://www.oecd.org/env/ehs/testing/section4-health-effects.htm).

Appendix 2: Procedural history

ECHA notes that the tonnage band for two members of the joint submission is 100 to 1 000 tonnes per year.

In your comments to the draft decision you have stated that you intend to transfer the lead role to one of the Member Registrants. In this regard, ECHA notes that in the teleconference on 1 December 2017 (communication number CCH-D-2114377741-43-01/D), you indicated a potential change in lead, where upon ECHA provided technical advice to you on how to change the role of the Lead Registrant in REACH-IT. However, in REACH-IT as of the time of referral of the decision to the MSCAs, you are assigned as the Lead Registrant for this registration dossier.

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 22 September 2017.

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

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

ECHA took into account your comments and 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.