EUROPEAN CHEMICALS AGENCY

Helsinki, 12 October 2016

Addressee: [redacted]

Decision number: CCH-D-2114343079-48-01/F
Substance name: 2-methylundecanal
EC number: 203-765-0
CAS number: 110-41-8
Registration number: [redacted]
Submission number: [redacted]
Submission date: 04.12.2014
Registered tonnage band: 100 to 1000 tonnes per year

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. **Vapour pressure (Annex VII, Section 7.5; test method: EU A.4/OECD TG 104) with the registered substance;**

2. **In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2, test method: EU B.10/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[1] or OECD TG 490[2]) with the registered substance provided that the study requested under 2. has negative results;**

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

5. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2; test method: EU B.26/OECD TG 408) in rats with the registered substance; and**

6. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2; test method: EU B.31/OECD TG 414) in a first species (rats or rabbits), 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 of the REACH Regulation. In order 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 an adequate and reliable documentation.

[1] Only the OECD TG is mentioned since it has recently been updated while the corresponding EU test method has not yet been updated.
[2] Only the OECD TG is mentioned since it has recently been adopted while the corresponding EU test method has not yet been published.

You are required to submit the requested information in an updated registration dossier by **19 April 2019.** You shall also 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. Advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall 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[3] by Hannu Braunschweiler, Head of Unit, Evaluation E1

[3] 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

Grouping of substances and read-across approach

In the registration, you have adapted the standard information requirements for

- *In vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2) or *in vitro* micronucleus study (Annex VIII, Section 8.4.2);
- *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3);
- Screening study for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.);
- Sub-chronic toxicity study (90-day; Annex IX, Section 8.6.2);
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2) in one species

by applying a read-across adaptation following REACH Annex XI, Section 1.5. In some cases you combine this read across approach with a weight of evidence argument (Annex XI, section 1.2).

The present section examines the read-across approach you have applied. Sections 2 to 6 of this Appendix examine whether your dossier fulfils the information requirements for the cases in which you applied the read across approach.

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use of information from structurally related substances (grouping of substances and read-across), "*provided that the conditions set out in Annex XI are met*".

Annex XI, 1.5. requires a structural similarity among the substances within a group or category so that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. Such predictions for properties need to be based on a similar or regular pattern of these properties as a result of the structural similarity. The following analysis presents your justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and an endpoint-specific context.

A. Description of the grouping and read-across approach proposed by the Registrant

Your read across approach is based on the claimed structural similarity of the registered substance 2-methylundecanal (target substance of the predictions based on the grouping and read-across approach) with:

- 1-dodecanal, used as analogue (source) substance to predict "no effects" for the results of a repeated dose toxicity study (90-day);
- nonanal, used as analogue (source) substance to predict the results of an *in vitro* sister chromatid exchange (SCE) and chromosomal aberration study and the results of an *in vitro* mammalian gene mutation study;
- 10-undecen-1-al, used as analogue (source) substance to predict "no mutagenic effect" for the results of an *in vivo* micronucleus study;
- heptanoic acid, used as analogue (source) substance to predict the "no adverse effects on offspring" for the results of a screening study for reproductive/ developmental toxicity and the results of a pre-natal developmental toxicity study;
- 2,6-dimethylhept-5-enal used as an analogue (source) substance to predict "no adverse effects on offspring" for the results of a screening study for reproductive/ developmental toxicity and the results of a pre-natal developmental toxicity study.

For each source substance you provide the same reason why you consider that that source substance can predict a property of the target substance: *"... the output from the OECD [Q]SAR Toolbox shows that the profiles of the Target Substance and the Source Substance are sufficiently similar such that available toxicological data from the Source Substance can be used to address the following endpoints in the REACH registration dossier for the Target Substance."*

You state: *"From the profile, it can be seen that the two substances share structural similarities and also "mechanistic action" similarities which are both general and endpoint specific."*

No explanation is however provided on what basis these analogue substances were selected for the individual properties listed above.

B. Information submitted by the Registrant to support the grouping approach and read-across hypothesis

You provided read-across justifications for each analogue substance listed above in section 13 of the IUCLID file. In these read-across documents you made a comparison of the outputs obtained from the OECD [Q]SAR toolbox to prove that the property profiles of the source substances and the target substance are sufficiently similar.

On this basis you conclude that the available toxicological data from the source substances can be used to address the selected properties for the target substance. The output parameters provided are generic substance descriptions (*e.g.* branched chain saturated aldehydes, non-metals), generic substance properties (*e.g.* DNA binding ability, protein binding ability, oestrogen receptor binding ability), and some information on Cramer class, eye irritation and skin irritation inclusions and exclusion rules of the BfR, a structural alert for aldehyde genotoxic carcinogenicity, and that the substances are bioavailable according to the Lipinski rule.

To compare the properties of the source substances with the target substance you also provided a data matrix for each pair. This matrix contains selected physico-chemical parameters (vapour pressure, partition coefficient, and water solubility) and acute toxicity values.

C. ECHA analysis of the grouping approach and read-across hypothesis in light of the requirements of Annex XI, 1.5.

ECHA understands that your strategy is to predict properties of the registered substance from different analogue substances. These analogue substances each have different structures when compared to each other. Consequently they also have different structural similarities and dissimilarities compared with the target substance. Nevertheless, you claim that each of the different analogue substances is structurally sufficiently similar to predict the selected property for the target substance.

In this regard ECHA notes that:

(1) The chemical structural similarity and dissimilarity of the individual substances is not connected scientifically to the attempted prediction. To make the prediction you claim for each source substance that it has a similar or the same effect compared to the target substance for the investigated test system. Such a claim needs a scientific explanation and supporting evidence. The scientific explanation offered is a vague reference to *"structural similarities and also "mechanistic action" similarities which are both general and endpoint specific"* based on the [Q]SAR toolbox output.

No further details are provided. This is insufficient for the reasons set out below:

(i) ECHA does not consider the offered reasoning a valid scientific explanation. The structural similarities and dissimilarities are not addressed and analysed. The "mechanistic action" similarity is based on a [Q]SAR prediction focussed on very few parameters. A reliable prediction for studies on mutagenicity, repeated dose toxicity or reproductive toxicity is not possible on this basis. Such studies investigate not only selected parameters but the complete interaction between the test substance and biological tissues and structures.

(ii) There are obvious major structural differences between the target substance and the substances heptanoic acid and 2,6-dimethylhept-5-enal. No further explanations are provided on why and how these structures allow predicting a complex property for the target substance such as reproductive toxicity (screening study, pre-natal developmental toxicity) with a very wide variety of biological targets (fertility, developing foetus, postnatal toxicity).

(iii) In addition, the possible effects of metabolites of the substance are investigated in such study types listed above. Mutagenicity studies have as integral part of the study design an experiment with an added organ tissue homogenate which is supposed to mimic the metabolic activation *in vivo*. The *in vivo* studies with intact animals have such metabolic activation inherently. A QSAR prediction based on structural alerts do not take into account all possible metabolic transformations of the target substance which may occur if the substance is subjected to mutagenicity testing. Therefore [Q]SAR parameter prediction based on the structures of the parent substance only cannot reflect the *in vivo* situation for substances subject to metabolism.

In conclusion no valid scientific explanation is offered why and how the specific structures of the source substances allow predicting the properties under consideration for the target substance. In particular, it is not explained why the structural differences and the metabolic fate of the substances would not influence the results of a toxicological test if conducted with the registered substance.

(2) Predictions for properties need to be based on a similar or regular pattern of these properties as a result of the structural similarity. You did not provide evidence in any case why and how they are based on a similar or regular pattern. The physico-chemistry data is not sufficient to prove that such pattern exists for mutagenicity studies (see endpoint section for specifics), repeated dose toxicity studies, screening study or pre-natal developmental toxicity study as well.

(i) The data matrices do not contain information on the properties investigating systemic effects after repeated administration. In terms of toxicity, only acute toxicity is included in the data matrix. Because repeated dose toxicity studies are not available on both the source and the target substance, it is not possible to compare systemic toxicity between the substances.
Therefore it is not possible to verify a similar or regular pattern as result of structural similarity for such predicted properties.

(ii) The source and target substances are likely to be taken up via all routes of administration and will be distributed in the systemic circulation. They will also be subject to metabolism in tissues, in particular the liver. You did not provide toxicokinetic data on absorption, distribution, metabolism and elimination of source and target substances.

It is therefore not possible to establish to which substances the test organism is exposed internally when exposed externally to the source or the target substance. Aliphatic substances are known to be metabolised via various oxidation steps at different positions of the alkyl chain. Depending on the chemical structure of the substances, different positions may be favoured resulting in different qualitative and quantitative metabolic patterns. As a consequence it is not possible without further data to verify that the same effects will occur qualitatively and quantitatively after exposure of source and target substances.

In conclusion, you have not established a similar or regular pattern as a result of structural similarity. Furthermore, no evidence has been provided which would support such patterns for the properties considered.

(3) Since you did not provide a transparent rationale for the selection of the analogue substances, ECHA cannot exclude bias in this selection. ECHA notes that there are a many other possible aldehyde structures which might be appropriate as source substances. Without further information on the rationale behind the analogue selection, ECHA cannot verify that you have selected the source substances which are most appropriate and furthermore that the source studies selected provide the most conservative estimate of the hazards.

(4) Some of the selected source studies are not compliant with Art 13 (3) and (4) and/or Annex XI, Section 1.1.2. This is addressed in the property specific section below.

D. Conclusion on the read-across approach

ECHA considers that structural similarity alone is not sufficient for predicting toxicological properties. It has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. ECHA notes that in view of the issues listed above it has not been demonstrated that the source and the target substances have the same properties or follow a similar pattern with regard to studies on mutagenicity, repeated dose toxicity, pre-natal developmental toxicity or reproductive toxicity (screening study). Besides a reference to the structural similarity there is no valid mechanistic explanation provided by you why predictions can be made using the results from the source substances. ECHA concludes that you have failed to meet the requirement of Annex XI, Section 1.5. that human health effects may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach).

Pursuant to Article 41(1) of the REACH Regulation, ECHA concludes that the adaptation of the standard information requirements for the properties investigated by the chromosomal aberration study *in vitro*, the mammalian gene mutation study *in vitro*, the repeated dose toxicity study (90-day) in rodents, the pre-natal toxicity studies in rats and rabbits, and the screening study for reproductive/developmental toxicity in the technical dossier based on the proposed read-across approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. Therefore, ECHA cannot accept those adaptations in the technical dossier that are based on Annex XI, Section 1.5.

1. Vapour pressure (Annex VII, Section 7.5.)

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

"Vapour pressure" is a standard information requirement as laid down in Annex VII, Section 7.5. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

Your technical dossier contains the following information:

i. Key study, accordingly to the "Gas saturation method" of the OECD TG 104 with the registered substance. A vapour pressure of 0.85 Pa at 20°C was reported.

ECHA observes, from the reporting in the endpoint study record, that you have only performed the experiment at a single temperature, 20 °C, calculating the Vapour pressure by using directly the formula given in the guideline. However, the OECD test guideline 104 requires that at least "two vapour pressure and temperature values" are measured to build a "log p versus 1/T curve" to "estimate the vapour pressure at 20 or 25°C". Moreover, the guideline recommends that if the "Gas saturation method is used, then the measured temperatures should be in the range of 120 to 150°C".

According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA. ECHA concludes that you did not follow the test guideline protocol and the flaws are sufficient to consider the result presented as invalid.

Furthermore, in the read-across justification document you report a vapour pressure of above 100 Pa, which is clearly higher than the reported value in the IUCLID endpoint study. This raises further uncertainty on the reported value.

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

In your comments on the draft decision, you have indicated that the study provided in the dossier *"fulfils all necessary validity criteria"*. As indicated already by ECHA above, the study provided reports a single vapour pressure value determined at only one temperature. The guideline requests the vapour pressure to be determined at various temperatures. This is a deviation from the guideline protocol which you did not justify in the provided study, nor on your comments to the draft decision.

Regarding the temperature range at which the measurements should be performed ECHA agrees with your comments. A range at lower temperatures than *"120 to 150 °C"* could be used, as long as the measured vapour pressures are in the range of the selected method.

In your comments you have also provided *"logP vs. 1/T curve with all boiling points under reduced pressure available in the free literature"*. This could be used in the dossier as supportive data, as indicated by you in the comments. However, this is not enough to fulfil the information requirements in isolation.

ECHA therefore still considers that the information provided on this endpoint for the registered substance does not meet the information requirement.

ECHA notes that you did not address in your comments the discrepancy between the value reported in the study and the value reported in the read-across justification document.

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: Vapour pressure (test method: EU A.4./OECD TG 104).

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

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

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.

Your technical dossier contains the following information:

i. key study, read-across from supporting substance (structural analogue or surrogate), Reliability 2 (reliable with restrictions), 1993, non-GLP, non-Guideline (Principle of the test: "*Rat hepatocytes cultured and exposed to test material, subsequently examined to sister chromatid exchanges (SCEs) and chromosome aberrations*"), Test material: Nonanal, CAS No 124-19-6, Composition and impurity of test material is unknown, Test concentrations up to 100 µM, No positive controls for clastogenicity, No metabolic activation. Your interpretation of the results: Negative for chromosome aberration, Positive for sister chromatid exchange;
ii. key study, read-across from supporting substance (structural analogue or surrogate), Reliability 2 (reliable with restrictions), 2007, GLP, OECD TG 474 (*In Vivo* mammalian erythrocyte micronucleus test), Test material: undec-10-enal, CAS No 112-45-8, Purity 97.7%, Tested doses 500, 1000, 2000 mg/kg/day. Your interpretation of the results: Negative.

ECHA considers that this information does not meet the standard information requirement for the reasons set out below.

First, you have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation.
However, as explained above in the section '*Grouping of substances and read-across approach*' of this decision, your adaptation of the information requirement cannot be accepted.

Second, with regard to the study in point i) above, ECHA notes that the study was not conducted according to the current test guideline.

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

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

(1) Adequacy for the purpose of classification and labelling and/or risk assessment;
(2) Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);

(3) Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) Adequate and reliable documentation of the study is provided.

ECHA notes that the study in point i) above has considerable deviations from the current test guideline (*e.g.* the study was not conducted according to GLP, no justification for the cells used, composition and impurity of test material unknown, no positive controls for clastogenicity, no metabolic activation).

Therefore, the study provided cannot be considered as a valid source study in your read-across approach.

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

In your comments on the draft decision you agreed to conduct the study.

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* cytogenicity study in mammalian cells (test method: EU B.10./OECD TG 473) or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487).

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

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

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. Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

Your technical dossier contains the following information:

i. key study, read-across from supporting substance (structural analogue or surrogate), Reliability 2 (reliable with restrictions), 1981, non-GLP, non-Guideline (Principle of the test: "*Mammalian cell gene mutation assay*" according to Clive & Spector (1975) *Mutation Research* Vol 31 pp 17-29),Test material: Nonanal, CAS No 124-19-6, Composition and impurity of test material is unknown, Test concentrations up to 100 nL/mL and 25 nL/mL without metabolic activation, Positive controls ethylmethanesulphonate and N-dimethylnitrosamine, No historical control data. Your interpretation of the results: Negative with and without metabolic activation.

ECHA considers that this information does not meet the standard information requirement for the reasons set out below.

First, you have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation. However, as explained above in the section '*Grouping of substances and read-across approach*' of this decision, your adaptation of the information requirement cannot be accepted.

Second, ECHA notes that the study provided was not conducted according to the current test guideline.

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

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

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

ECHA notes that the reporting detail in the robust study summary is not sufficient for a detailed comparison with the current test guideline.

Despite the reporting deficiency, ECHA makes the following observations: a) it is unclear how the methodology used compares to the modern guideline; b) composition and impurity of test material is unknown; c) the justification of the top doses is not provide; d) there is not sufficient information on cytotoxicity; and e) there is no historical control data form the test laboratory.

Therefore, the study provided cannot be considered as a valid source study in your read-across approach.

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

In your comments on the draft decision you agreed to conduct the study.

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 2. has negative results.

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

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

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

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

Your technical dossier contains the following information:

i. Weight of evidence, read-across from supporting substance (structural analogue or surrogate), Reliability 2 (reliable with restrictions), 1990, GLP, non-guideline (Guideline: "*Unclear; makes reference to FDA (1987)*", Principle of the test: "*1 week treatment followed by 7 d cohabitation period through gestation, parturition and 4-d postpartum period*"), Test material: 2,6-dimethylhept-5-enal, CAS No 111-14-8, Composition and impurity of test material is unknown, oral:gavage, Doses tested: 300, 1500, 3000 mg/kg/day, females only. Your interpretation of the results: NOAEL (P) 300 mg/kg/day;
ii. Weight of evidence, read-across from supporting substance (structural analogue or surrogate), Reliability 2 (reliable with restrictions), 1990, GLP, non-guideline (Guideline: "*Unclear; makes reference to FDA (1987)*", Principle of the test: "*1 week treatment followed by 7 d cohabitation period through gestation, parturition and 4-d postpartum period*"), Test material: heptanoic acid, CAS No 111-14-8, Composition and impurity of test material is unknown, oral:gavage, Doses tested: 200, 1000, 2000 mg/kg/day, females only. Your interpretation of the results: NOAEL (P) 200 mg/kg/day;

ECHA considers that this information does not meet the standard information requirement for the reasons set out below.

First, you have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation. However, as explained above in the section '*Grouping of substances and read-across approach*' of this decision, your adaptation of the information requirement cannot be accepted.

Second, ECHA notes that the study provided was not conducted according to the current test guideline.
According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA.

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

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

ECHA notes that the reporting detail in the robust study summary is not sufficient for a detailed comparison with the current test guideline. Despite the reporting deficiencies ECHA has identified the numerous deficiencies of the studies when compared with the current OECD 421 test guideline.

The deficiencies include: a) Composition and impurity of test material is unknown, b) The study was conducted in females only the current guideline requires investigation of both sexes; c) The rats were dosed for 7 days the current guideline requires that the animals are dosed throughout the study (*i.e.* approximately 54 days for females and a minimum of 28 days for males); d) There is no histological examinations of ovaries, testes and epididymides; and e) There is no information on gestation length, number of live births and post-implantation loss; number pups with grossly visible abnormalities, number of runts; time of death during the study or whether animals survived to termination; number of implantations, litter size and litter weights, etc.

Therefore, none of the studies can be considered as a valid source study for your read-across approach.

Third, ECHA notes that you have indicated that the two studies constitute a weight of evidence for this endpoint. However, you have not justified as to how and why the provided information constitutes a sufficient weight of evidence leading to the assumption/conclusion that a substance has or has not a particular dangerous property for the key parameters investigated in an OECD 421 study. Furthermore, ECHA notes that, as highlighted in the previous paragraph, both studies provided have the same deficiencies.

Therefore, your adaptation of the information requirement can neither be accepted on this basis.

For these reasons, 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 guideline is designed for use with the rat and the substance is administered orally unless other routes of administration are considered more appropriate.

In your comments on the draft decision you agreed to address the information requirement by conducting the study. You propose to meet the standard information requirements of Annex VIII, Section 8.7.1. and Annex IX, Section 8.6.2. by conducting a single study. This study would be a combination of a Screening study for reproductive/developmental toxicity (OECD TG 422) and a Sub-chronic toxicity study (90-days; OECD TG 408). An outline of an experimental protocol for this combined study was provided in the comments on the draft decision.

With regard to the proposed combination of the requested OECD TG 422 and OECD TG 408, ECHA considers that the outline of the proposed combined study is not detailed enough for ECHA to form a view on the acceptability of such approach. Nevertheless ECHA makes the following observations: i) the proposed study design seems to be based on an outdated

version of the OECD TG 422. In the latest update of the test guideline (28 July 2015), the pups (and dams) are investigated on post-natal day 13; ii) the number of females in each dose group proposed in your proposal deviates from the recommended number given in the OECD 422 TG which state "*that each group be started with at least 10 males and 12-13 females*"; and iii) the proposed study design does not account for the fact that the OECD 408 TG states that "*The females should be nulliparous and non-pregnant*". In addition, ECHA notes that you, in the outline of the combined study, propose to conduct histopathological examinations that include staging of spermatogenesis.

ECHA considers that if the study is combined and it is your intention to generate additional information on reproductive toxicity potential of the registered substance as part of the combined study that additional examinations of male and female reproductive parameters may be included.

ECHA considers that you may combine the two studies and incorporate additional examinations of reproductive parameters under your own discretion as long as the combined study does not compromise the integrity of either study designs outlined in the OECD TG 408 or OECD TG 422; or any of the parameters foreseen to be investigated by the respective test guidelines. In particular, ECHA considers the following aspects will need to be addressed in your study protocol if you combine the study types:

i) follow the latest version of the <u>both</u> the OECD TG 408 and the OECD TG 422;
ii) include separate groups of non-pregnant females animals which are necessary to comply with the OECD TG 408;
iii) to include a demonstration that the dose setting for the OECD TG 408 part of the study has not been compromised by the fact that the study will contain pregnant animals; and that the results of the OECD TG 408 study are adequate and relevant for the derivation of applicable DNELs and/or risk assessment; and
iv) to generate additional information on reproductive toxicity potential include the following additional parameters: additional examinations of male and female reproductive parameters (oestrous cycle, sperm parameters, and reproductive and other certain organs and tissues) that produce respective information as outlined for P parental animals in EU test method B.35, sections 1.5.3., 1.5.4. and 1.5.6. to 1.5.8.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit information derived with the registered substance subject to the present decision: Reproductive/developmental toxicity screening test (test method: OECD TG 421) in rats by the oral route; <u>or</u> Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (test method: OECD TG 422) in rats by the oral route.

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

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH 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.

Your technical dossier contains the following information:

i. Key study, read-across from supporting substance (structural analogue or surrogate), Reliability 1 (reliable without restrictions), 2012, GLP, OECD TG 408, Test material: dodecanal, CAS No 112-54-9, Purity > 98.6%, oral:feed, Doses tested: 200, 2000, 6000 and 20000 ppm (equivalent to a mean achieved dose of 14.6, 143.8, 430.8 and 1409.7 mg/kg bw/day). Your interpretation of the results: NOAEL 20000 ppm.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation. However, as explained above in the section '*Grouping of substances and read-across approach*' of this decision, your adaptation of the information requirement cannot be accepted.

For this reason, 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. The information provided in the technical dossier and the chemical safety report on properties of the registered substance and its uses indicate that human exposure to the registered substance by the inhalation route seems to be less relevant. More specifically, the substance is used as an odour agent in mixtures with industrial, professional and consumer uses with spray applications (concentration [redacted]%). However, the substance is in the liquid state with reported very low vapour pressure of about 0.85 Pa; there is currently no repeated dose toxicity study available on the registered substance and ECHA considers that that systemic effects need to be investigated; and there is currently no information that indicates route-specific effects following inhalation exposure which would prevent route-to-route extrapolation. Therefore, ECHA considers that the oral route - which is the preferred one as indicated in ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.5.4.3 - is the most appropriate route of administration. Hence, the test shall be performed by the oral route using the test method OECD TG 408/EU B.26.

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.

In your comments on the draft decision you agreed to conduct the study. You propose to meet the standard information requirements of Annex VIII, Section 8.7.1. and Annex IX, Section 8.6.2. by conducting a single study (for response to comments see point 4 above).

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.

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

Pursuant to Articles 10(a)(vi) and/or (vii), 12(1)(d) and 13(4) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation.

A "pre-natal developmental toxicity study" 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. You provided the following justification for the adaptation: *"The test substance was assessed for toxicity to reproduction using a one-generation study in rats on the analogue substances 2,6-dimethylhept-5-enal and Heptanoic acid. The results showed that under the conditions of the test, dose levels of 300 mg/kg bw/day of 5-heptenal, 2,6-dimethyl and dose levels of 200 mg/kg bw/day of Heptanoic acid had no adverse effects on the reproductive performance of female Sprague-Dawley rats or the growth or development of their offspring.*
In addition, acute oral toxicity testing (LD50 > 5000 mg/kg) and acute dermal toxicity testing (LD50 > 8000mg/kg) suggests that 2-methylundecanal is of low toxicity. The expected route of exposure to this substance is considered to be dermal rather than oral or inhalation, which suggests that systemic exposure via the dermal route would be low. Further developmental toxicity testing is not deemed appropriate. The evidence does not support the necessity to perform additional animal studies".

You have labelled this waiving statement as 'study scientifically unjustified'.

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement. ECHA understands this adaptation argument as a Weight-of-Evidence adaptation according to Annex XI, Section 1.2. However, ECHA notes that this adaptation does not meet the general rules for adaptation of Annex XI, Section 1.2. for the following reasons:

a) Your read-across approach has been rejected, as explained above in the section *'Grouping of substances and read-across approach'* of this decision. Therefore, studies conducted on the proposed analogue substance cannot be considered as predictive for the properties of the registered substance subject to this decision. In addition, the studies provided on the proposed *analogue substances 2,6-dimethylhept-5-enal and Heptanoic acid* have not investigated the same key parameters as those investigated in a pre-natal developmental toxicity study (OECD TG 414) and can therefore not be compliant with Art 13 (3) and (4) and/or Annex XI, Section 1.1.2.;
b) The acute toxicity studies do not investigate the same key parameters as those investigated in a pre-natal developmental toxicity study (OECD TG 414). ECHA notes that the acute toxicity may be low, however, low acute toxicity is not considered to be predictive of low systemic toxicity or absence of developmental toxicity; and
c) You have not justified as to how and why the provided information constitutes a sufficient weight of evidence leading to the assumption/conclusion that a substance has or has not a particular dangerous property for the key parameters investigated in an OECD 414 study.

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

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.
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. Based on this default consideration, ECHA considers testing should be performed with rats or rabbits as a first species.

According to the test method EU B.31/OECD TG 414, the test substance is usually administered orally. On the basis of this default consideration, ECHA considers testing should be performed by the oral route.

In your comments on the draft decision you indicate that a pre-natal developmental toxicity study (OECD TG 414) may not be required depending on the results of the requested studies on mutagenicity and reproductive toxicity. In addition, you suggest a weight-of-evidence adaptation based on a hypothetical outcome of the requested studies.

With regard to your first comment that the requirement of the study is dependent on the outcome of other studies requested in this decision, ECHA highlights that the timeline given in the draft decision allows for sequential testing where appropriate. Column 2 of Annex IX, Section 8.7 clearly list under what condition a Pre-natal developmental toxicity study is not required. Should the outcome of the requested studies on mutagenicity and reproductive toxicity be that the substance meets these conditions of Column 2 of Annex IX, Section 8.7; then it is possible to provide in the dossier an adaptation on this basis and a pre-natal developmental toxicity study would not be required.

With regard to your proposed weight of evidence adaptation, you provide the following information: i) That no effect on reproductive and developmental toxicity would be observed in the requested OECD TG 421/422 study; ii) "*The metabolism of branched-chain aldehydes such as 2-methylundecanal is expected to follow that of other branched chain alcohols and aldehydes. Metabolism is primarily via oxidation and the formation of the corresponding carboxylic acid. The branched chain acid is then metabolised via beta oxidation in the longer branched chain followed by cleavage to yield linear acid fragments, which are completely metabolised in the fatty acid pathway or the tricarboxylic acid cycle (WHO, 1998)*"; and iii) That 2-methylundecanal would be negative in the requested genotoxicity assays and thus malformations in offspring caused by genetic damage would not be expected. You provide no further justification.

Irrespective of the possible final arguments you provide in an updated dossier ECHA considers that your proposed adaptation does currently not meet the general rules for adaptation of Annex XI, Section 1.2., because it is not possible to assume/conclude based on this information that the registered substance has or does not have hazardous properties with regard to pre-natal developmental toxicity. This is because: i) information from a OECD 421/422 is not sufficient to meet the standard information requirement of a pre-natal developmental toxicity study (OECD TG 414) due to the lower statistical power of the test and that the test does not investigate the same key parameters; ii) a generic argument about metabolic fate of a class of substances does not provide additional adequate information with regard to pre-natal developmental toxicity, and iii) teratogenicity effects are not solely caused by genotoxicity, thus, lack of genotoxicity does not exclude developmental toxicity.

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 (rats or rabbits) by the oral route.

Deadline to submit the requested information in this decision

In your comments on the draft decision you agreed to provide the requested information according to the given deadline.

Appendix 2: Procedural history

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

The compliance check was initiated on 1 October 2015.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation:

ECHA notified you of the draft decision and invited you to provide comments. ECHA took into account your comments, which were sent within the commenting period, and they are reflected in the Reasons (Appendix 1).

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment(s).

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

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

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-48 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

2. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) 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 substance used for the new test(s) 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 composition 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 substance tested in the new test(s) 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 test(s) must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.