EUROPEAN CHEMICALS AGENCY

Helsinki, 14 September 2018

Addressee: [redacted]

Decision number: CCH-D-2114440086-55-01/F
Substance name: 2-Oxetanone, 3-C12-16-alkyl-4-C13-17-alkylidene derivs.
EC number: 284-932-5
CAS number: 84989-41-3
Registration number: [redacted]
Submission number: [redacted]
Submission date: 21/08/2017
Registered tonnage band: Over 1000

## DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

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

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

3. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. / OECD TG 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102 with the registered substance;**

4. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance, provided that the study requested under 3. has a negative result;**

5. **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;**

6. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a second species (rat or rabbit), oral route with the registered substance;**

7. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce some toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.**

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 ***22 March 2021***. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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

**Appeal**

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] by 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.

ECHA
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**Appendix 1: Reasons**

INFORMATION ON SUSBTANCE IDENTITY

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

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

Name or other identifier of the substance is an information requirement as laid down in Annex VI, Section 2.1 of the REACH Regulation. The name and other identifiers are used to identify the substance in an unambiguous manner and are therefore fundamental for substance identification. Adequate information needs to be present in the registration dossier for the registered substance to meet this information requirement.

You identified the registered substance as of Unknown or Variable composition, Complex reaction products or Biological materials (UVCB). Information required to be provided according to Annex VI, Section 2.1 of the REACH Regulation on the naming of UVCB substances such as the registered substance shall consist of two parts: (a) the chemical name and (b) a more detailed description of the manufacturing process, as indicated in section 4.3 of the "*Guidance for identification and naming of substances under REACH and CLP*" (May 2017, Version 2.1), referred hereafter as the "SID Guidance".

a) The chemical name:

According to chapter 5 of the SID Guidance, a UVCB substance with a narrow distribution of constituents is not regarded as equal to a UVCB substance with a broader composition and *vice versa*. The information provided in the registration dossier should thus provide an unambiguous description of the substance under consideration.

The EC and CAS entries, as well as the chemical name "(4E)-4-(C13-C17)alkylidene-3-(C12-C16)alkyloxetan-2-one" included in section 1.1 of the registration dossier refer to a substance with carbon chain lengths of C12-C16 (in position 3) and C13-C17 in (position 4). However, this specification is inconsistent with the information provided on both the reported composition of the substance (Section 1.2 of the dossier) and the analytical data (Section 1.4 of the dossier). Indeed, the molecular and structural information of the constituents reported in section 1.2 may indicate that the carbon chain lengths of the starting materials are [redacted], while the unreacted fatty acids are identified in section 1.2 as "[redacted]". In addition, according to table 6 of the analytical report with filename [redacted], attached in section 1.4 of the registration dossier, only [redacted] and [redacted] chains are present in the substance constituents.

Furthermore, the chemical name "(4E)-4-(C13-C17)alkylidene-3-(C12-C16)alkyloxetan-2-one" also indicates a specific geometry (E as opposed to Z) around the [redacted] double bond. However, the information provided both in section 1.2 (reported composition) and in section 1.4 (analytical data) does not refer to the double bond geometry of [redacted] and its oligomers.

Based on the inconsistencies currently present in the registration, and in the absence of further information on the manufacturing process of the substance (see below), ECHA concludes that the current chemical name and the corresponding EC entries do not represent an appropriate description of the registered substance. Indeed, based on the

information currently included in your dossier, the carbon chain lengths and the geometry around the double bond are not confirmed by the analytical data.

Accordingly, you are requested to clarify the identity of the registered substance by providing a chemical name that is representative of the substance which is the subject of this registration. The chemical name provided must be consistent with the compositional information reported in section 1.2 and with the analytical data reported in section 1.4. More specifically, in case when the chemical name refers to a specific geometry of the double bond (e.g. E), the description of the method used to establish the geometry of the double bond as reported in the chemical name should be provided as required according to the Annex VI, Section 2.3.7. You are advised to consult chapter 4.3. for specific guidance on the naming of UVCB substance. You shall report the chemical name of the UVCB substance in the "IUPAC name" field in section 1.1 of the IUCLID dossier.

b) The manufacturing process description:

According to chapter 4.3.1 of the SID Guidance, UVCB substances shall be identified by their name, the identity of the starting material(s) and the most relevant steps taken during processing.

ECHA notes that the information provided in your registration dossier regarding the manufacturing process does not allow an unambiguous description of the substance identity. Indeed, section 1.2 of the registration dossier does not include information on the ratio of reactants and on relevant operating parameters. In addition, you state that the substance is a "[redacted]", whilst the first step of the process involves "[redacted]".

ECHA therefore notes that there are inconsistencies in terms of the identity of the starting materials used and in the description of the steps of the manufacturing process, especially in terms of the identity of the starting materials used and the process steps.

Accordingly, you are requested to provide more specific information on the manufacturing process of the registered substance, including a detailed composition of the starting materials used, of the ratio of reactants, and of any relevant operating parameters (e.g. parameters used to determine the completion of reaction) and a reaction scheme including all reactions and process steps.

The description of the manufacturing process of the registered substance should be included in the "Description of the composition" field in Section 1.2 of the IUCLID dossier.

In case the current numerical identifiers are not appropriate to describe the registered substance, you should not remove or modify at this stage the EC entry in the inventory fields of the IUCLID technical dossier. To ensure unambiguous identification of the registered substance, you should however indicate, in the "Remarks" field of the reference substance in IUCLID section 1.1, the following: "The EC number 284-932-5 currently assigned does not specifically correspond to the registered substance. This identifier cannot be modified or deleted at this stage in the present registration update for technical reasons". You should also specify, in the same "Remarks" field, any available and appropriate EC number for the substance. Any available CAS entry for the registered substance should be reported under the "CAS information" header of the reference substance in Section 1.1 of the IUCLID dossier.

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

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

In that case, ECHA will inform you in due time as to when and how the identifier adaptation process shall be initiated. In any case, you should note that the application of the process of adapting the identifier does not affect your obligation to fulfil the requirements specified in this decision.

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

The substance composition corresponds to the chemical representation of what the substance consists of and is therefore an essential part of substance identification and the cornerstone of all the REACH obligations. In that respect and according to chapter 4.3 of the SID Guidance, the following applies for UVCB substances:

- All constituents present in the substance with a concentration of ≥ 10 % shall be identified and reported individually;
- All known constituents and constituents relevant for the classification and/or PBT assessment of the registered substance shall be identified and reported individually;
- Other constituents shall be identified as far as possible by a generic description of their chemical nature;
- For each constituent or group of constituents, the typical, minimum and maximum concentration levels shall be specified.

You have reported several groups of constituents in section 1.2 of the registration dossier: [redacted]. However, as explained in section 1.a above, ECHA notes that the information provided is inconsistent with the information provided on both the name other identifiers of the substance (Section 1.1 of the dossier) and the analytical data (Section 1.4 of the dossier).

Accordingly, you are requested to revise the composition information to align it with the naming and other identifiers of the registered substance (Section 1.1 of the dossier) and the analytical information included in the registration dossier (Section 1.4 of the dossier), especially with regard to the description of the carbon chain length.

TOXICOLOGICAL INFORMATION

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Your registration dossier contains for multiple endpoints adaptation arguments in the form of a grouping and read-across approach according to Annex XI, 1.5. of the REACH

Regulation. ECHA has assessed first the scientific and regulatory validity of your Grouping and read-across approach in general before the individual endpoints (sections 3 to 7).

**Grouping and read-across approach for toxicological information**

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

- *in vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- *in vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- toxicity for reproduction (Annex X, Section 8.7.3.)

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 and toxicological 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 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 properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. A specific justification must be provided for each endpoint relying on a read-across adaptation.

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, 2-Oxetanone, 3-C12-16-alkyl-4-C13-17-alkylidene derivs. (EC number 284-932-5, CAS RN 84989-41-3), using data of the structurally similar substance, 2-Oxetanone, 3-(C14-16 and C16-unsatd. branched and linear alkyl) 4-(C15-17 and C17-unsatd. branched and linear alkylidene) derivs. or "P-2290" (EC number 434-710-0, CAS RN 849705-80-2) (hereafter the "source substance").
However, there is no justification supporting your read-across hypothesis. Therefore, your dossier is lacking a basis for predicting relevant human health properties of the registered substance from data for the source substances. In the absence of this information, ECHA cannot verify that the properties of the registered substance can be predicted from the data on the source substance.

[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.

Hence, you have not established that relevant properties of the registered substance can be predicted from data on the analogue substance.

Since your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5., it is rejected and it is necessary to perform testing on the registered substance.

In your comments on the draft decision, you provided a read-across justification document that originates from an earlier version of the registration dossier. ECHA has evaluated the information provided in this document and considers that it does not adequately demonstrate that the toxicological properties of the registered substance may be predicted from the properties of the selected source substance. More specifically, the justification document does not provide a scientific justification as to why the 4-ring unsaturated lactone should be considered as the determinant of the toxicological properties of the target and source substance (as stated in the justification document).

In addition, the document does not address how the structural differences between the source and target substances may impact the prediction of the toxicological properties of the target substance. You indicated that you will seek to stengthen the read-across justification in order to adapt the information requirement on *in vitro* gene mutation in bacteria (Annex VII, Section 8.4.1.), *in vitro* gene mutation in mammalian cells (Annex VIII, Section 8.4.3.) and pre-natal developmental toxicity (Annex IX, Section 8.7.2.). You also specified that if an appropriate adaptation of the information requirement according to Annex XI, section 1.5 cannot be provided, you will conduct the requested studies.

Further guidance on how to develop and report a read across justification can be found in the ECHA Read-Across Assessment Framework[3]. This document foresees that there are two options which may form the basis of the read-across hypothesis: (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).

### 3. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

An "*In vitro* gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

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

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

(1) Adequacy for the purpose of classification and labelling and/or risk assessment;

[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).

(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.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a test according to OECD TG 471 and GLP with the analogue substance, 2-Oxetanone, 3-(C14-16 and C16-unsatd. branched and linear alkyl) 4-(C15-17 and C17-unsatd. branched and linear alkylidene) derivs. (EC number 434-710-0, CAS RN 849705-80-2). The test was conducted in 1999 in five strains and was assigned a reliability score of 1.

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

You have also provided three supporting studies performed with the registered substance from the years 1988 and 1992 with reliability scores of 2. They were performed similarly to OECD TG 471 and to GLP standard.

The supporting studies with the registered substance used four different strains of *S. typhimurium*, TA 1535, TA 1537, TA 98 and TA 100, and they did not include tests with strains *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101). However, since the tests were conducted, significant changes have been made to OECD TG 471 so that additionally testing with *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101) is now required. Therefore, the provided study does not meet the current guideline, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation.

ECHA concludes that a test using *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102 has not been submitted and that the test using one of these is required to conclude on *in vitro* gene mutation in bacteria.

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

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to complete the following information derived with the registered substance subject to the present decision: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471) using one of the following strains: *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102.

In your comments on the draft decision you specified that you will seek to strengthen the read-across justification in order to adapt the information requirement related to this endpoint. You also acknowledged that you will consider performing the requested study if the read-across adaptation cannot be adequately justified.

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

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing a non-guideline HGPRT assay (2010) performed according to OECD 476 and GLP with an analogue substance, 2-Oxetanone, 3-(C14-16 and C16-unsatd. branched and linear alkyl) 4-(C15-17 and C17-unsatd. branched and linear alkylidene) derivs. (EC number 434-710-0, CAS RN 849705-80-2), in CHO cells. The study was concluded as not mutagenic in the HPRT locus assay under *in vitro* conditions in CHO cells in the absence and the presence of metabolic activation.

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

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.

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

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian cell gene mutation test (test method: OECD TG 476 or OECD TG 490) provided that the study requested under Section 3. has a negative result.

In your comments on the draft decision you specified that you will seek to strengthen the read-across justification in order to adapt the information requirement related to this endpoint. You also acknowledged that you will consider performing the requested study if the read-across adaptation cannot be adequately justified.

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

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 the information requirement for a pre-natal developmental toxicity study in a first species according to Annex XI, Section 1.5. of the REACH Regulation by providing a study record for a developmental toxicity study (similar to OECD TG 414) with the analogue substance, 2-Oxetanone, 3-(C14-16 and C16-unsatd. branched and linear alkyl) 4-(C15-17 and C17-unsatd. branched and linear alkylidene) derivs. (EC number 434-710-0, CAS RN 849705-80-2), performed in the rabbit.

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

In addition, while you have not explicitly claimed the following to be an adaptation, you have also provided information that could be interpreted as an attempt to adapt the information requirement according to Annex IX, Section 8.7.2., column 2. In that respect, you provided a study record for a "combined repeated dose toxicity study with the reproduction/ developmental toxicity screening test" (test method: OECD TG 422) with the registered substance. However, this study does not provide the information required by Annex IX, Section 8.7.2. because it does not cover key parameters of a pre-natal developmental toxicity study like examinations of foetuses for skeletal and visceral alterations. Therefore, your adaptation of the information requirement is rejected. ECHA further notes that adequate and reliable documentation of the study is not provided.

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

According to 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 wax-like 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.

In your comments on the draft decision you specified that you will seek to strengthen the read-across justification in order to adapt the information requirement related to this endpoint. You also acknowledged that you will consider performing the requested study if the read-across adaptation cannot be adequately justified.

*Note for your consideration*

ECHA notes that a revised version of OECD TG 414 was adopted this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. You should test in accordance with the revised 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).

The above note also applies to Appendix 1, section 6 (pre-natal developmental toxicity study in a second species request), of the present decision.

### 6. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

Pre-natal developmental toxicity studies (test method EU B.31./OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

You have sought to adapt the information requirement for a pre-natal developmental toxicity study in a second species according to Annex XI, Section 1. You provided the following justification for the adaptation *"In accordance with Section 1, Annex XI of the REACH regulation 1907/2006, studies do not need to be conducted if it does not appear scientifically necessary"*.

Your rationale for the adaptation is as follows:

1. the registered substance is not classified;
2. the main likely route of exposure is dermal, and you attempted to demonstrate with information from an analogue substance that dermal absorption is very low;
3. no developmental effect is seen in first species (rabbit) with the analogue substance.

However, ECHA notes that your 3 arguments do not meet any of the general rules for adaptation of Annex XI, Section 1. In addition your read-across approach according to Annex XI, Section 1.5. is rejected as explained above in Appendix 1 of this decision under "Grouping and read-across approach.

ECHA notes that your adaptation does not meet either the specific rules for adaptation of Annex X, Section 8.7., column 2, for the following reasons: the registered substance is not a genotoxic carcinogen, or a germ cell mutagen, since it bears no corresponding classification. The substance is not classified as toxic for reproduction categopry 1A or 1B.

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 consideration, ECHA considers testing should be performed with rabbits or rats as a second species, depending on the species tested in the first pre-natal developmental toxicity study.

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 wax-like 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 second species (rabbit or rat) by the oral route.

In your comments on the draft decision, you acknowledged that you agree to conduct the requested study and you propose to use the rat as the test species. However, you specified that you will only conduct the study if, based on the data provided on pre-natal developmental toxicity in a first species, the registered substance does not meet the criteria for classification as toxic for reproduction category 1B.

ECHA refers to the notes for consideration below.

*Notes for your consideration*

You are reminded that before performing a pre-natal developmental toxicity study in a second species you must consider the specific adaptation possibilities of Annex X, Section 8.7., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species with other available information enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement.

## 7. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

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

*a) The information provided*

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 a dose range finding study with the analogue substance, 2-Oxetanone, 3-(C14-16 and C16-unsatd. branched and linear alkyl) 4-(C15-17 and C17-unsatd. branched and linear alkylidene) derivs. (EC number 434-710-0, CAS RN 849705-80-2). You indicated that this dose range study is for a "*main fertility reproductive function study*", and consequently does not fulfil the requirement of Annex X, Section 8.7.3. However, as explained above in Appendix 1 of this decision under "Grouping and read-across approach", your adaptation of the information requirement is rejected.

Furthermore, this study does not provide the information required by Annex X, Section 8.7.3. because it does not cover key elements, such as exposure duration, life stages and statistical power of an extended one-generation reproductive toxicity study. More specifically, the main missing key elements are: 10 weeks pre-mating exposure duration, at least 20 pregnant females per group, and an extensive postnatal evaluation of the F1 generation.

In the technical dossier you have also provided a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD TG 422) on the registered substance. However, this study does not provide the information required by Annex X, Section 8.7.3. because it does not cover key elements, such as exposure duration, life stages and statistical power of an extended one-generation reproductive toxicity study. More specifically, the main missing key elements are: 10 weeks pre-mating exposure duration, at least 20 pregnant females per group, and an extensive postnatal evaluation of the F1 generation. Therefore, your adaptation of the information requirement is rejected.

Finally, while you have not explicitly claimed the following to be an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex IX, Section 8.7.3., column 1, since you gave the following argumentation: "*The criteria for not performing the extended one generation reproductive*

*toxicity study (OECD 443) are met and therefore further testing for this endpoint is not required since: 1. No direct effects on fertility in an OECD 422 with* [redacted] *(rather general organs inflammation). 2. No effects on reproductive organs in 90 day repeated dose studies with* [redacted] *and the structural analogue* [redacted] *3. No effects on fertility in a preliminary reproductive performance study with the structural* [redacted] *) up to and including a dose of 1000 mg/kg. The extended one generation reproductive toxicity test is waived on the basis of the availability of an OECD 414 pre-natal developmental toxicity study showing no cause for concern. The test substance did not reveal any teratogenic potential up to and including a dosage of 1000 mg/kg bodyweight/day."*

However, ECHA notes that since your substance is registered at more than 1000 tonnes per year, as a minimum, the information specified in column 1 of Section 8.7.3., Annex X. is required. Therefore your adapatation according to Annex IX, Section 8.7.3., column 1, is not applicable.

In addition, your adaptation does not meet either the criteria of the specific rule for adaptation of Annex X, Section 8.7., column 2, for the following reasons: the registered substance is not a genotoxic carcinogen, or a germ cell mutagen, since it bears no corresponding classification. The substance is not classified as toxic for reproduction categopry 1A or 1B. Furthermore following administration, there is systemic absorption as demonstrated by effects observed in the repeated dose toxicity studies. Finally, there is also significant human exposure, as reported in your registration dossier. Hence the criteria of the specific rule for adaptation of Annex X, Section 8.7., column 2 are not met. Therefore, your adaptation of the information requirement is rejected.

Consequently all three pieces of information provided on this endpoint for the registered substance in the technical dossier, whether taken separately or together, do not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

Thus, an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. is required. The following refers to the specifications of this required study.

*b) The specifications for the study design*

*Premating exposure duration and dose-level setting*

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6. (version 6.0, July 2017). Based on the information you provided, the registered substance has a log Kow > 4.5. Accordingly, the ten-week exposure duration is supported and maintained, to ensure that the steady state in parental animals has been reached before mating.

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a conducted range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

*Species and route selection*

According to the test method EU B.56./ OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in 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 wax-like solid, ECHA concludes that testing should be performed by the oral route.

c) Outcome

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: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.

In your comment on the draft decision, you explained that you agree to address the information gaps in the dossier. You specified that you consider that this study should only be conducted once the results of the pre-natal developmental toxicity study in rats will be available. You consider that the results of such study may impact the design of the extended one-generation reproductive toxicity study. You further state that providing the requested information within the 30 months deadline may be feasible as long as no complications occur during the experimental phase.

In order to consider modifications to the deadline in the draft decision ECHA requires a justification for the design of the testing strategy including explicit documentation on the length of the studies. This may include , for example, letters from CROs explaining why you propose a specific length of time for each study. ECHA notes that you did not provide such documentation. ECHA furthermore notes that the timeline provided in the decision allows the sequential testing. Accordingly, ECHA did not modify the aforementioned deadline.

*Notes for your consideration*

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no

triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the new information shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6. (version 6.0, July 2017). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

## 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 12 October 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 request(s) or the deadline.

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.