Helsinki, 18 May 2020

Addressees
Registrants of "C14-17 alkanes, sec-mono- and disulfonic acids, phenyl esters" listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
16 July 2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: c14-17 alkanes, sec-mono- and disulfonic acids, phenyl esters
EC number: 701-257-8
CAS number: NS

Decision number: [Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/D)]

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***25 November 2022***.

A. Requirements applicable to all the Registrants subject to Annex VII of REACH

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method EU B.13/14. / OECD TG 471) with the Substance

2. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method EU C.3./OECD TG 201) with the Substance

B. Requirements applicable to all the Registrants subject to Annex IX of REACH

1. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method EU C.20./OECD TG 211) with the Substance

2. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method OECD TG 210) with the Substance

C. Requirements applicable to all the Registrants subject to Annex X of REACH[1]

1. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route, specified as follows:
   - Ten weeks premating exposure duration for the parental (P0) generation;
   - Dose level setting shall aim to induce systemic toxicity at the highest dose level;
   - Cohort 1A (Reproductive toxicity); and
   - Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation which shall be followed to weaning.

   You must report the study performed according to the above specifications. Any expansion of the study must be scientifically justified.

Conditions to comply with the requests

You are bound by the requests for information corresponding to the REACH Annexes applicable to your own registered tonnage of the Substance at the time of evaluation. You have to comply with the requirements of Annexes VII to X of REACH, if you have registered a substance at above 1000 tpa.

Appendices A to C state the reasons for the requests for information to fulfil the requirements set out in the respective Annexes of REACH.

Appendix E: Observations and technical guidance addresses the general requirements for the selection and reporting of the test material used to perform the required studies. It also provides generic recommendations and references to ECHA guidance and other reference documents.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information. The timeline has been set to allow for sequential testing, where applicable.

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] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

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

Appendix A: Reasons for the requests to comply with Annex VII of REACH

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 1 to 10 tonnes or more per year must contain, as a minimum, the information specified in Annex VII to the REACH Regulation.

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.);

An *In vitro* gene mutation study in bacteria is a standard information requirement in Annex VII to REACH.

You have provided a key study in your dossier:

- *In vitro* salmonella/microsome test similar to OECD TG 471 ([redacted] 1981)

We have assessed this information and identified the following issue(s):

To fulfil the information requirement, the study has to meet the requirements of OECD TG 471 (1997). One of the key parameter(s) of this test guideline include:

a) The test must be performed with 5 strains: four strains of *S. typhimurium* (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101)

The study you have provided was not conducted with the appropriate 5 strains as the information provided does not include results in the required fifth strain, S. *typhimurium* TA102 or E. *coli* WP2 uvrA or E. *coli* WP2 uvrA (pKM101).

In your comments to the draft decision you have provided a weight of evidence adaptation under Annex XI, section 1.2 of REACH. To support your adaptation, you provided the following information:

i. *In vitro* salmonella/microsome test referred to above and already provided in your dossier. You agreed that this study covers only four strains instead of the required 5 strains.
ii. An argument why "*the conduction of an Ames test with 5 strains* [...] *is not necessary and should be omitted*" for your Substance. You indicated that your Substance does not have oxidising properties, it is not a hydrazine derivative and it does not have reactive functional groups, which could act as a cross-linking agent. You conclude, that testing in the 5th strain for that purpose, in accordance with paragraph 13 of the OECD TG 471, is not needed.
iii. Structural alerts from QSAR Toolbox Profilers (OASIS: DNA binding and DNA alerts for Ames; OECD: DNA binding; ISS: In vitro mutagenicity (Ames) alerts) using a claimed representative structure of the UVCB substance. You conclude that no alert was found with any of the QSAR Toolbox profilers, and that the mechanistic and empiric profiler for Ames mutagenicity are negative.

We have assessed the information and identified the following issues:

Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or

has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

According to ECHA Guidance R.4.4, a weight of evidence adaptation involves an assessment of the relative values/weights of different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance of the information for the given regulatory information requirement. Subsequently, relevance, reliability, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

You have not provided any assessment of the relative values/weights of different sources of information provided.

In spite of this critical deficiency, ECHA has nevertheless assessed the provided sources of information:

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.4.1. at Annex VII includes the effect of the substance, with and without metabolic activation, on the number of revertant colonies of five strains of bacteria: four strains of S. typhimurium (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either E. coli WP2 uvrA, E. coli WP2 uvrA (pKM101) or S. typhimurium TA102.

> The source of information (i.) provides relevant information on four strains of bacteria (S. typhimurium (TA98; TA100; TA1535; TA1537 or TA97a or TA97)). However, as already indicated above, it does not include the results of the fifth strain.
>
> With source of information (ii.) you argue that the missing 5th strain is not needed for your Substance for the reasons explained above. However, you have misinterpreted the meaning of paragraph 13 of OECD TG 471. Most importantly, it requires that at least five strains of bacteria are used. As regards the missing 5th strain, it does not detect exclusively oxidising mutagens, cross-linking agents and hydrazines, it can also demonstrate the effect of other types of substances. In addition the 5th strain detects mutations at AT base pairs (while the four standard S. typhimurium strains detect mutations at GC base pairs)[2,3,4] . Therefore, the argument you provided does not stand and does not remove the obligation to provide relevant information on the missing 5th strain.
>
> QSAR Toolbox Profilers (source of information (iii)) are not scientifically valid (Q)SAR models, and therefore the results from these Profilers cannot be used to indicate the presence or absence of a certain dangerous property under Annex XI, section 1.3 of REACH. QSAR Toolbox Profilers can be used to identify analogue substances and apply

[2] Wilcox, P. et al. (1990). Comparison of Salmonella typhimurium TA 102 with Escherichia coli WP2 Tester strains. Mutagenesis, 5, 285-291. (NB: it is the reference 19 mentioned in paragraph 13 of OECD TG 471 of 1997.
[3] Gatehouse DG et al. (1994). Recommendations for the performance of bacterial mutation assays. Mutat Res. 1994 Jun;312(3):217-33.
[4] Levin DE et al. (1982) A new Salmonella tester strain (TA102) with AT base pairs at the site of mutation detects oxidative mutagens. Proc. Nadl Acad. Sci. USA, Genetics, Vol. 79, pp. 7445-744

the grouping and read-across approach if the conditions under Annex XI, section 1.5. are fulfilled.

Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide a justification for the read-across including a hypothesis, explanation of the rationale for the prediction of properties and robust study summary(ies) of the source study(ies).[5]

You have provided neither a justification for a read-across adaptation (hypothesis and explanation of the rationale for the predictions), nor robust study summaries of studies conducted with identified analogue substances. In addition, you have not demonstrated that the claimed representative structure used in the QSAR Toolboox Profilers can be used to cover all constituents of the UVCB substance.

Therefore, in light of these deficiencies the source of information (iii) does not provide relevant and reliable information for this endpoint.

Based on the above, you have not provided information on the number of colonies with and without metabolic activation for the fifth strain (either E. coli WP2 uvrA, E. coli WP2 uvrA (pKM101) or S. typhimurium TA102), which would establish whether your Substance causes mutagenic effects in bacteria.

Therefore, it cannot be concluded whether your Substance has or has not this hazardous property. Your adaptation according to Annex XI, Section 1.2. is rejected and the information requirement is not fulfilled.

2. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.);

Growth inhibition study aquatic plants is a standard information requirement in Annex VII to REACH.

You have provided a key study according to EU Method C.3 ([redacted] 2003), conducted with the Substance.

OECD TG 201 is the preferred guideline to fulfil this information requirement. The guideline specifies that for difficult to test substances (such as poorly water-soluble and adsorptive), following the specifications given in the OECD Guidance 23 is required. The OECD 201 and the OECD GD 23, require(s) that you must (among others):

- provide evidence that the test solution preparation allowed achieving the maximum dissolved concentration under test conditions. In particular, justify the separation technique especially if filtration is used, as it can cause losses due to adsorption onto the filter matrix;
- provide analytical monitoring to verify the initial concentrations and maintenance of the exposure concentrations during the test;
- provide evidence that exposure concentrations have been maintained throughout the test (within ±20 % of the nominal or intial measured concentration).

In cases where no analytical monitoring has been conducted and only nominal concentrations are provided, the data are acceptable only if the test concentrations are likely to have been

[5] ECHA Guidance R.6, Section R.6.2.6.1

maintained. These circumstances may occur if the substance has the following properties: abiotically stable, non volatile, soluble in water (concentration is well below its limit of solubility) and if it has low adsorption to either delivery apparatus or the exposure vessels.[6] The use of nominal concentrations must be justified and documented in the dossier.

The Substance can be considered poorly/sparingly water-soluble and adsorptive (reported LogKow of 5.7-11.3), and it is therefore a 'difficult to test' substance.

You report that the test solutions were prepared by addition of the test substance to dilution water (2 mg/L), followed by stirring for 24 h and removal of solid components by filtration using a folded filter (pore size 7-12 µm). You have not provided any justification for the methods used to prepare the test solutions.

You have not carried out any analytical monitoring of the test concentrations. You have claimed that: "*due to inherent properties of the test item no substance specific analysis could be established in the concentration range given.*" However, you have not specified what are those inherent properties and how they make a substance specific analysis impossible.

You provided results expressed in terms of nominal concentrations (2 mg/L) with the following justification: "*as the test item is stable against hydrolysis and scored as not volatile, a constant test item concentration throughout the study can be assumed.*" You have not considered the potential losses due to adsorption.

You have not justified nor demonstrated that the method applied in the aquatic toxicity test, including the use of filter as a separation method and stirring time of 24-h, allowed achieving maximum dissolved concentrations.

You have not provided analytical monitoring nor any evidence that the exposure concentrations have been maintained. As described above, analytical monitoring is required.

In your comments to the draft decision you claim that in this algae study the test concentrations were likely maintained. To support your claim, you indicate that in a fish and in an invertebrate study with analytical monitoring, the test concentrations varied less than 20% from the nominal values.
However, ECHA notes that no analytical monitoring was conducted in any of the fish and aquatic invertebrates studies available in the dossier and you do not provide any other evidence to justify your claim. Therefore, your claim is not substantiated.

Nevertheless, in your comments you agree that the exposure concentrations could deviate from the nominal or initial test concentrations. Therefore, you propose to conduct a preliminary study to provide evidence that for the existing algae study the test solution preparation was adequate and the exposure concentrations were maintained.

We have assessed this information and identified the following issues.

In order to provide evidence whether the test solution preparation and the exposure concentrations met the requirements of OECD TG 201 and the OECD GD 23 as listed above, in the preliminary studies[7] the test solutions must be prepared under conditions equivalent (in terms of test medium, pH, test vessels, preparation procedures, etc.) to those used in the toxicity test i.e. algae growth inhibition. In addition, to demonstrate stability of the test

[6] ECHA Guidance R.7b, Section R.7.8.4.1
[7] For example, solubility experiment as explained in section 7.1.1 of OECD GD 23 and preliminary stability study as explained in section 5.2 of OECD GD 23

chemical, samples of the test solution should be analysed at the beginning and typically at 24-hour intervals for the duration of the test period.

You indicate that you will conduct this preliminary test at the highest test concentration in Long-term toxicity testing on aquatic invertebrates (section B.1 below). You also indicate that you will use the same test substance application as in the algae study and monitor the test concentrations.

You intention to conduct a preliminary study during Long-term toxicity testing on aquatic invertebrates does not seem suitable in order to prove that the test solution preparation and the exposure concentrations met the requirements of OECD TG 201 and the OECD GD 23 for the algae toxicity test. As explained above, it is necessary to prepare test solutions using the same preparation conditions as the existing algae test. You also have not specified the concentration nor the duration of the proposed preliminary test. You have also not indicated the sampling frequency for the analytical monitoring to demonstrate the stability of the test substance throughout the algae test.

Unless these conditions are followed closely as explained above, the preliminary study cannot serve to provide evidence that the test solution preparation method allowed achieving the maximum dissolved concentration and that the exposure concentration was maintained throughout the test (within ±20 % of the nominal or initial measured concentration).

Since there is currently no evidence that in the available algae growth inhibition study the test solution preparation and exposure concentrations met the requirements of OECD TG 201 and the OECD GD 23 as listed above, the request for a new study remains.

Therefore, the information requirement is not fulfiled.

Appendix B: Reasons for the requests to comply with Annex IX of REACH

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII-IX to the REACH Regulation.

1. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.)

Long-term toxicity testing on aquatic invertebrates is a standard information requirement in Annex IX to REACH.

You have adapted this information requirement with the following: "*According to the REACh Annex XI, Section 1, a test on long-term toxicity towards invertebrates does not need to be conducted as it is scientifically not necessary. Vertebrate-animal testing can be avoided as no additional information is gained through that test. Information gained through ecotoxicological testing is commonly used in the scope of classification and labeling (C&L), the PBT assessment as well as the chemical safety assessment. (..) To draw conclusions on the chemical safety assessment, standard testing data on short-term toxicity for three trophic levels is available. Based on these results and the intrinsic substance properties, the test substance is neither classified as dangerous for the environment, nor classified as a PBT substance. The risk of the test substance to the aquatic compartment can thus be sufficiently described based on the available data and with respect to the Guidance Document R.7b (ECHA, 2008), no further assessment is required.*"

We have assessed this information and identified the following issue(s):

A. In order to adapt the standard testing regime according to Annex XI, Section 1, you have to provide scientific data and justification.

   You have not specified which general rule for adaptation of Annex XI, Section 1 you specifically refer to and you have not provided any scientific data or justification to fulfil its conditions.

   Therefore, the provided adaptation is rejected.

B. To adapt the information requirement for long-term toxicity to aquatic invertebrates based on Annex IX, Section 9.1, Column 2, the Chemical Safety Assessment (CSA) needs to assess and document that risks arising from the Substance are controlled (Annex I, Section 0.1). In particular, you need to take into account the following element(s) described in Annex I:

   - Environmental hazard assessment including classification and labelling and identification of PNEC.

   The toxicity information should at least cover species of three trophic levels: algae/aquatic plants, invertebrates (Daphnia preferred), and fish.[8] For substances with low solubility and hydrophobic properties, risks cannot be reliably assessed based on short term toxicity tests (i.e. to derive a reliable PNEC for this substance).[9] Such substances require longer time to be significantly taken up by the test organisms and as a consequence steady state conditions are likely not reached within the duration of a short-term toxicity test. For this

[8] ECHA Guidance R.7b, Section R.7.8.5.3
[9] ECHA Guidance R.7b, Section R.7.8.4.3

reason, short-term tests may not give a true measure of toxicity for this type of substances and long-term effects cannot be excluded.

Based on the information you provided, the Substance is hydrophobic (Log Kow 5.7-11.3), which indicates that it has low water solubility.

You have provided short term toxicity studies, and no long term studies on daphnia or fish.

As indicated above, short-term studies are, due to the properties of the Substance, insufficient to assess the risks.

Consequently, the CSA does not allow to conclude that the risks to the aquatic environment are controlled. Therefore, the provided adaptation is rejected.

Based on the above, the information you provided does not fulfil the information requirement.

In your comments to the draft decision you agree to conduct the requested study.

You further indicate your intention to conduct a preliminary test at the highest test concentration within this requested study, using the same test substance application as in the algae study (section A.2 above). As explained under section A.2 above, since the Substance is difficult to test you must demonstrate the achievement of maximum dissolved concentration and maintainment of the exposure concentration also in the requested long-term *Daphnia* study. ECHA stresses that if for this endpoint you intend to use a preliminary test as evidence to demonstrate the adequacy of the test solution preparation and the stability of the test substance, you must follow the same conditions that will be used in the requested toxicity study, i.e. Long-term *Daphnia* study, for the same reasons as explained under section A.2 above.

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

Long-term toxicity testing on fish is a standard information requirement in Annex IX to the REACH Regulation.

You have adapted this information requirement with the following: "*According to the REACh Annex XI, Section 1, a test on long-term toxicity towards invertebrates does not need to be conducted as it is scientifically not necessary. Vertebrate-animal testing can be avoided as no additional information is gained through that test. Information gained through ecotoxicological testing is commonly used in the scope of classification and labeling (C&L), the PBT assessment as well as the chemical safety assessment. (..) To draw conclusions on the chemical safety assessment, standard testing data on short-term toxicity for three trophic levels is available. Based on these results and the intrinsic substance properties, the test substance is neither classified as dangerous for the environment, nor classified as a PBT substance. The risk of the test substance to the aquatic compartment can thus be sufficiently described based on the available data and with respect to the Guidance Document R.7b (ECHA, 2008), no further assessment is required.*"

We have assessed this information and identified the same issues as discussed under request B.1. above.

For the reasons explained under request B.1. above, the hazard assessment is not complete, and consequently the CSA does not allow to conclude that the risks to the aquatic environment

are controlled. Therefore, the provided adaptation is rejected.

In your comments to the draft decision you propose a testing strategy for long-term aquatic toxicity testing starting first with the long-term toxicity study on aquatic invertebrates (request B.1 above), and then considering the need for long-term toxicity testing on fish, based on some assumptions that you make in your comments.

We have assessed the information provided and identified the following issues.

Regarding long-term toxicity testing, there are no further requirements for fish testing if there is compelling evidence to suggest that the fish is likely to be at least a factor of about 10 less sensitive than invertebrates or algae. In case of poorly water soluble substances, acute toxicity tests cannot serve for this purpose, for the same reasons as explained in request B.1 above. In case the relative sensitivity of fish cannot be predicted, further testing is needed.[10]

Compelling evidence to compare the species sensitivites must be based on data that are relevant for this endpoint, which include investigations of lethal and sub-lethal effects.

In your comments to the draft decision, you explain that if the Substance will show no effects in the long-term toxicity study on aquatic invertebrates (request B.1 above), you assume the Substance will likely not cause chronic effects also to fish.

In order to substantiate the expected lack of chronic effects to fish, you indicate that in the available fish bioaccumulation study with the Substance, no effects towards fish were observed after 36 days of exposure at a test concentration of 1 mg/L.

ECHA notes, that you have not justified how and why the outcome of the long-term *Daphnia* study can be used as evidence to compare the species sensitivities that is relevant to the current endpoint.

Regarding the absence of effects in the fish bioaccumulation study, ECHA notes that bioaccumulation studies do not provide information on the effect endpoints foreseen to be investigated for the current endpoint. As given in par. 51 of OECD TG 305, bioccumulation studies are performed using aqueous exposure concentrations that must be below concentrations that pose a toxicity concern. It is also required by the validity criteria that mortality or other adverse effects are below 10% at the end of the test (par. 24 of OECD TG 305). Therefore, the absence of effects observed in the fish bioaccumulation study does not constitute relevant evidence to compare the species sensitivities.

Due to the above, there is no compelling evidence to predict the relative sensitivity of fish and long-term testing on fish is needed.

Based on the above, the information you provided does not fulfil the information requirement.

[10] ECHA Guidance R.7b, Section R.7.8.5.3

Appendix C: Reasons for the requests to comply with Annex X of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier at a tonnage abve 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to REACH.

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

The basic test design of an Extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is a standard information requirement under Annex X to REACH. Furthermore Column 2 of Section 8.7.3. defines when the study design needs to be expanded.

You have provided

(i) a weight of evidence adaptation in accordance with Annex XI, section 1.2.
(ii) a non-guideline fertility study (labelled as "other information"; Bornmann, 1956)

We have assessed this information and identified the following issue(s):

A. Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

For a weight of evidence approach to be considered sufficient it must cover the particular dangerous (hazardous) properties of the Substance foreseen to be investigated in an EOGRT study with the test design as requested in this decision, i.e. with extension to mate the Cohort 1B animals to produce the F2 generation.
Information on sexual function and fertility (functional fertility and histopathology of reproductive organs and tissues) similar to extension of Cohort 1B (i.e. mating of Cohort 1B animals to produce the F2 generation) must be provided because the criteria at Annex X section 8.7.3 column 2 are met, see the Specifications for the study design below.

In your justification for the weight of evidence approach the following independent sources of information (lines of evidence) are presented:

i. a one-generation reproductive toxicity study (key study according to OECD TG 415; [redacted] 2002)
ii. a sub-chronic toxicity study (OECD TG 408; [redacted] 1987)

You have not provided any source of information which investigates sexual function and fertility in the F1 generation (producing the F2 generation). Thus ECHA cannot evaluate the possible hazard to sexual function and fertility of the offspring.

You acknowledge in your comments that the IUCLID dataset did not contain sufficient information for an independent assessment of the provided studies. You provided, in your comments, additional information regarding the results of the above mentioned studies and general arguments based on additional literature references, as follows:

Regarding OECD TG 415 study by [redacted] (2002):
a. The premating exposure of this study was 10-weeks;

b. Results on the evaluation of sperm parameters in F0 males was conducted in this study;
c. Results of oestrous cycle staging was perfomed in F0 females;
d. Results of developmental milestones in the F1 weanlings (including historical control data);

Regarding OECD TG 408 study by [redacted] (1987):
e. No histopathological effects on reproductive organs (organ weight data not provided).

General agrument based on additional litterature references:
f. Regarding rodent histopathological evaluation, you refer to literature and claim that histopathological examinations in repeated dose studies are of high value and high sensitivity for evaluation of reproductive toxicity.

Based on all of the above you argue that the information provided covers the key parameters of the OECD TG 443 and that further testing is not necessary because the substance is not toxic to reproduction and there are no indications of endocrine activity.

You consider "*according to Annex XI section 1.2*" that there is sufficient weight of evidence to conclude that the Substance is not toxic to reproduction and that there is no indication for endocrine activity. However, sources of information you provided do not give information on the particular dangerous (hazardous) properties of the Substance foreseen to be investigated in an EOGRT study with the test design as relevant for your Substance and explained further below, and as requested in this decision, i.e. with extension to mate the Cohort 1B animals to produce the F2 generation. Specifically, the information provided give sufficient information about 'systemic toxicity' and 'sexual function and fertility' in the parental generation but not in the offspring (F1 generation) or the F2 generation.

In conclusion, the sources of information as indicated above, do not cover all relevant life stages required in an OECD TG 443, as the extensive post-natal investigations of the fully exposed F1 generation up to the adulthood are not included in any of the sources of information. In addition, the criteria for extension of the Cohort 1B are met for the Substance according to column 2 of Annex X, Section 8.7.3., as described below, and information for those properties is not covered by any of the sources of information that you provided.

ECHA has assessed the information provided in your comments:

- Regarding point a., the fact that the OECD TG 415 was conducted with a 10-week premating exposure makes some of the parameters measured in the OECD TG 415 comparable to the same parameter measured in the OECD TG 443. However, the number of parameters measured in the OECD TG 415 is very limited compared to the OECD TG 443; this applies to all life-stages investigated in the study both parental animals and their offspring.
- Regarding point b., c., the OECD TG 415 provides sufficient information regarding sperm parameters and oestrus cyclicity in parental (P) generation. However, information regarding these two key parameters are still missing for the F1 generation.
- Regarding point e., f., ECHA considers the histopathological investigations in an OECD TG 408 comparable to the investigations foreseen to be conducted on the parental (P) generation. However, information regarding histopathological

investigations are still missing for the F1 generation. In addition, histopatological examinations is not the only aspect of reproductive toxicity, reproductive toxicity studies also provide information regarding functional fertility of the parental generations and potential toxicity to the offspring though gestation and early postnatal development. Histopathological examinations in a repeated dose toxicity study conducted on adult rats do not address these key aspect of reproductive toxicity

Accordingly, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 443 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

B. With respect to the non-guideline fertility study, ECHA has evaluated this study under Annex, Section XI 1.1.2. although you do not explicitly claim an adaptation. This adaptation rule enables registrants to claim that the data from experiments not carried out according to GLP or the test methods referred to in Article 13(3) can be considered equivalent to data generated by those test methods. However, a number of conditions need to be met, including:

1. Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
2. Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3);

The study you provided does not meet the above conditions, for the following reasons:

1. The key parameters of an EOGRTS as specified in this decision are not met because relevant life stages have not been investigated: the animals were not exposed during gestation, lactation, *in utero* and postnatally up to adulthood. Furthermore, key parameters of sexual function and fertility have not been examined: e.g. sperm parameters have not been investigated in P0 and F1 animals, and histopathology of the gonads (P0 and F1) is missing.

2. The exposure duration of the provided fertility study is "six weeks before mating" for the female F0 animals. This is not comparable to the requirements of an continuous exposure from at least ten weeks before mating until the end of lactation for the parental (P0) generation, and continuous exposure of the F1 generation starting from *in utero* and continuing postnatally up to adulthood as well as during extension of Cohort 1B until termination of F2 generation.

Your comments acknowledge that the non-guideline fertility study (Bornmann, 1956) *"is not comparable and not sufficient regarding the examined parameters compared with actual requuirements for multi-generation studies".* You also state that the study was included in IUCLID with a reliability score of 4 (unassignable) for the sake of completeness. You still consider that this study provides some relevant information regarding the general physical development of the offspring.

ECHA has assessed the information provided in your comments and notes the following:

a. The study may provide some relevant information regarding general physical

development. However, due to severe limitations in the study design this information is by no means conclusive or sufficient when compared to the OECD TG 443 as requested in this decision. The limitations in the study design include: only 8 females treated (OECD TG 443 requires 20 females per dose group), only one dose group (OECD TG 443 requires three dose groups), only the parental females were exposed for six weeks before mating, i.e. the animals were not exposed during gestation, lactation, *in utero* and post-natally up to adulthood; therefore, the filial generations were not exposed to the Substance (OECD TG 443 requires continuous exposure). The study provides some information on female reproductive function following six weeks of premating exposure; this information is similar to what is observed in the females of the OECD TG 415. However, the study does not provide any information on pre-, post natal effects on the offspringas required by the OECD TG 443.

b. You consider the reliability of the study is so low that it is unassignable. According to the Guidance R.4, page 10: In general, some types of data that are not reliable (i.e. those where insufficient documentation exist for making an assessment) and data for which it is not possible to assign reliability, may only be used as supporting data.

ECHA considers that the study by Bornmann (1956) is not reliable and cannot contribute individually or collectively, with the sources of information discussed under point A) above, to the fulfilment of this information requirement.

a) The specifications for the study design

Premating exposure duration and dose-level setting

The length of premating exposure period must be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on sexual function and fertility.

Ten weeks premating exposure duration is required if there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA Guidance[11]. In this specific case ten weeks exposure duration is supported by the lipophilicity of the Substance (logKow = 5.7) to ensure that the steady state in parental animals has been reached before mating.

Therefore, the requested premating exposure duration is ten weeks.

The highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs. If there is no relevant data to be used for dose level setting, it is recommended that range-finding results are reported with the main study.

You have to provide a justification with your study result that demonstrates that the dose level selection meets the conditions described above.

Cohorts 1A and 1B

[11] ECHA Guidance R.7a, Section R.7.6.

Cohorts 1A and 1B belong to the basic study design and shall be included.

Extension of Cohort 1B

If the Column 2 conditions of 8.7.3., Annex X are met, Cohort 1B must be extended.

The extension is inter alia required, if the use of the registered substance is leading to significant exposure of consumers and professionals (column 2, first paragraph, lit. (a) of Section 8.7.3., Annex X and

- if there are indications that the internal dose for the registered substance will reach a steady state in the test animals only after an extended exposure (column 2, first paragraph, lit. (b), second indent of Section 8.7.3., Annex X), or
- there are indications of one or more relevant modes of action related to endocrine disruption from available *in vivo* studies or non-animal approaches (column 2, first paragraph, lit. (b), third indent of Section 8.7.3., Annex X.

The use of the Substance is leading to significant exposure of professionals because the Substance is used by professionals e.g. in adhesives and sealants, coatings and paints, thinners, paint removes as well as cleaning and rinsing fluid (PROCs 9, 10, 11).

In addition, there are indications that the internal dose for the Substance will reach a steady state in the test animals only after an extended exposure. Specifically, the $\log K_{ow}$ for the substance is above 4.5 indicating potential accumulation.

In your comments, you argue that toxicokinetic information demonstrates that 10 week pre-mating exposure duration is sufficient and that the F2 generation is not needed. However, you state that the toxicokinetics data show a half-life of 8 days after single dose, and a half-life of 15 days after repeated dosing. According to ECHA Guidance R.7a, "duration of longer than a week to reach the steady state may be considered as extended". This triggers a 10-week premating exposure duration for the EOGRTS, and it is also a trigger the extension of Cohort 1B to produce F2 generation.

Furthermore, there are indications of one or more modes of action related to endocrine disruption because changes in parameters sensitive to endocrine activity are observed. More specifically, the provided one-generation reproductive toxicity study (OECD TG 415) showed a delay in balano-preputial separation as well as a delay in vaginal opening in F1 animals.

In your comments on the draft decision, you consider that the delays in balano-preputial separation and vaginal opening are secondary to the retarded body weight development, and also refer to the historical control data. ECHA considers that in both males and females there is a clear trend as the delays (days) are dose-dependent whereas the body weight changes are not. Statistical significance is reached only at the two highest doses in males, and in the high dose in females. Furthermore, you also acknowledge in your comments, the high-dose males exceed the historical control data. Moreover, in your comments you argue that an endocrine activity can be excluded; because one would expect balano-preputial separation and vaginal opening to move in opposite directions if the Subsrance have endocrine activity. You do not specify hormone action you refer to. ECHA disagrees with this statement because, at the time of puberty, circulating oestradiol levels increase and stimulate vaginal opening. A reduction or delay in the pre-pubertal increase in oestradiol can cause a delay ion vaginal opening. Any substance with anti-oestrogenic properties (i.e. it counter acts the effects of oestrogen) could cause the same effects. Balano-preputial separation an external sign of

sexual development in male rats which may be used as an index of change in per-ipubertal androgen secretion. It does not inform on the underlaying reasons for the altered androgen secretion. ECHA does not consider the observed results as contradictorary but rather as an indication of altered sex hormone metabolism which manifests itself differently in males and females.

Therefore, ECHA considers the effects observed in balano-preputial separation and vaginal opening as "indications of one or more relevant modes of action related to endocrine disruption" which is one of the conditions for extension of Cohort 1B to produce the F2 generation, as noted above.

In addition you argue that, F2 generation is not needed. To support your claim you have submitted literature references which make a generic argument that producing a F2 generation very rarely provides critical information, so it cannot be regarded as a key parameter for risk assessment or classification and labelling. ECHA disagrees with this statement, according to the CLP regulation the hazard class for reproductive toxicity includes any effect of the substance that has the potential to interfere with sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring. The F2 generation investigates sexual function and fertility in adult males and females of the F1 generaltion, following life-long exposure to the substance, and in addition developmental toxicity in the offspring. As effects observed may form the basis for classification, such investigations then constitute key parameters. In addition in this specific case, there are Substance-specific concerns stemming from delays in sexual development of the offspring and indications of one or more endocrine modes of action.

Therefore, Cohort 1B must be extended.

The F2 generation shall be followed to weaning allowing assessment of nursing and lactation of the F1 parents and postnatal development of F2 offspring.

Species and route selection

The study shall be performed in rats with oral[12] administration.

Further expansion of the study design

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 Cohorts 2A and 2B and/or Cohort 3 if relevant information becomes available from other studies or during the conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance[21].

[12] ECHA Guidance R.7a, Section R.7.6.2.3.2.

Appendix D: Procedural history

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 24 July 2018.

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

ECHA took into account your comments and amended the requests as explained below.

Specifically, the requests for information regarding water solubility (Annex VII, section 7.7.) and bioaccumulation (Annex IX, Section 9.3.2. in conjunction with Annex I, Section 3.1.5) have been removed.

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix E: Observations and technical guidance

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

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 the Member States.

3. Test guidelines, GLP requirements and reporting

   Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

   Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses shall be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

   Under Article 10 (a) (vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide: 'How to report robust study summaries[13]'.

4. Test material

   Selection of the test material(s) for UVCB substances

   While selecting the test material you must take into account the impact of each constituent/impurity on the test results for the endpoint to be assessed. For example, if a constituent/impurity of the Substance is known to have an impact on (eco)toxicity, the selected test material must contain that constituent/impurity. Any constituent that has a harmonised classification and labelling, according to the CLP Regulation (Regulation (EC) No 1272/2008) must be identified and quantified using the appropriate analytical methods.

   The OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 11 [ENV/MC/CHEM(98)16] requires a careful identification of the test material and description of its characteristics. The Test Methods Regulation (EU) 440/2008, as amended by Regulation (EU) 2016/266, requires that "*if the test method is used for the testing of a* [...] *UVCB* [...], *sufficient information on its composition should be made available, as far as possible, e.g. by the chemical identity of its constituents, their quantitative occurrence, and relevant properties of the constituents*".

   In order to meet this requirement, all the constituents of the test material used for each test shall be identified as far as possible. For each constituent the concentration value in the test material shall be reported in the Test material section of the endpoint study record.

   Technical reporting of the test material for UVCB substances

[13] https://echa.europa.eu/practical-guides

The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers" on the ECHA website[14].

5. List of references of the ECHA Guidance documents[15] and OECD Guidance documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 in this decision.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[16]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

[14] https://echa.europa.eu/manuals
[15] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[16] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

OECD Guidance documents[17]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.
Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No 43, referred to as OECD GD 43.

[17] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix F: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fufilled
[redacted]	[redacted]	[redacted]