ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 26 November 2018

Addressee: [redacted]

Decision number: CCH-D-2114449848-30-01/F
Substance name: Reaction mass of p-t-butylphenyldiphenyl phosphate and bis(p-t-butylphenyl) phenyl phosphate
List number: 939-505-4
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 28/11/2016
Registered tonnage band: 100-1000

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. **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), with the registered substance;**

2. **In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method: OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2, test method: OECD TG 487) with the registered substance;**

3. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490), with the registered substance, provided that both studies requested in 1 and 2 have negative effects ;**

4. **Sub-chronic neurotoxicity study (90-day), oral route (Annex IX, Section 8.6.2., Column 2; test method: EU B.43./OECD TG 424) in rats, combined with the sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) with the registered substance, as specified in Appendix I, section 4.**

5. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rat or rabbit), oral route, with the registered substance;**

6. **Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: Daphnia magna reproduction test, EU C.20./OECD TG 211) with the registered substance;**

7. **Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210) with the registered substance.**

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

You have to submit the requested information in an updated registration dossier by ***3 December 2020***. You also have to update the chemical safety report, where relevant.

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.

Appendix 1: Reasons

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13 (3) and (4) of REACH.

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 paragraph 13 of the current OECD TG 471 test guideline (updated 1997) at least five strains of bacteria should be used: S. typhimurium TA1535; TA1537 or TA97a or TA97; TA98; TA100; S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). This includes four strains of S. typhimurium (TA1535; TA1537 or TA97a or TA97; TA98; and TA100) that have been shown to be reliable and reproducibly responsive between laboratories. These four *S. typhimurium* strains have GC base pairs at the primary reversion site and it is known that they may not detect certain oxidising mutagens, cross-linking agents and hydrazines. Such substances may be detected by *E.coli* WP2 strains or *S. typhimurium* TA102 which have an AT base pair at the primary reversion site.

In the technical dossier you have provided a test from the year 1978 according to OECD TG 471 and GLP with an assigned reliability score of 2. The test used several different strains of *S. typhimurium* TA 1535, TA 1537, TA 1538, TA 98 and TA 100 and it did not include tests with strains S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). However, since the test was conducted, significant changes have been made to OECD TG guideline 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 updated OECD guidelines, nor can it be considered as providing equivalent data according to the conditions in Annex XI, section 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 appropriately conclude on *in vitro* gene mutation in bacteria.

In addition, in your provided study record ([redacted] 1978), you stated that the study is not performed according to GLP, and is equivalent or similar to a TG method (OECD TG 471) with deviations. You stated that the test is performed on the registered substance, but also that the "*Chemical identity of test substance [is] not reported*". ECHA notes that in the technical dossier you did not provide any specific details on the test material used in the study.

The use of existing data on human health properties, from experiments not carried out according to GLP or the test methods referred to in Article 13(3), is considered valid so long as the conditions of Annex XI, section 1.1.2 are met. This study does not have adequate and reliable coverage of the key parameters foreseen to be investigated in the OECD TG 471, specifically (1) the identification data (if known), physical nature and purity of the test material are not provided (2) triplicate plating should be used at each dose level, and there were not replicates in this experiment. In addition, there is not adequate and reliable

documentation because you have not provided tabulation of the results, nor historical negative (solvent/ vehicle) and positive control data, with e.g. ranges, means and standard deviations. ECHA concludes that the conditions of Annex XI, section 1.1.2 are not met, and consequently this study does not provide the information required by Annex VIII, Section 8.4.1.

The technical dossier does not contain any other adaptation in accordance with column 2 of Annex VIII, Section 8.4.1. or with the general rules of Annex XI for this standard information requirement.

Therefore 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.

In your comments to the draft decision you underlined that the test material is called "Santicizer 154" and "Phosflex 51B" which are the commercial names of the product described in dossier of EC 700-990-0. ECHA notes that the test material is not the substance subject to this decision. Further, you express the intention to address the requests in this decision by further developing a read across adaptation based on a worst-case approach linked to the presence of triphenyl phosphate which is present at comparatively much lower amounts in the (proposed target) substance subject to this decision compared to the proposed source (EC 700-990-0). ECHA observes that the you did not provide a read-across hypothesis which addresses the request or documentation according to the general rules of Annex XI, section 1.5. The documentation that you provided in your comments does not contain any specific justification whereby relevant human health properties of the registered substance may be predicted from data for the source substances nor have you provided data which would support your worst-case approach. 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. Moreover, and as explained above, the provided study does not meet the updated OECD guidelines criteria (at least five strains of bacteria should be used including strain S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101)). Further, this study does not have adequate and reliable coverage of the key parameters foreseen to be investigated in the OECD TG 471 and there is no adequate and reliable documentation. Therefore ECHA concludes that this study does not provide the information required by Annex VIII, Section 8.4.1.

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: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471).

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information

specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

An "*In vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study" is a standard information requirement as laid down in Annex VIII, Section 8.4.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier you have provided a study record for an *in vitro* chromosome aberration study using a guideline "equivalent or similar to OECD TG 479" ("Sister chromatid exchange assay in mammalian cells and *In vitro* mammalian chromosome aberration test"). This key study ([redacted] 1979; reliability score of 2) is not performed according to GLP, and is equivalent or similar to a TG method (OECD TG 479) with deviations. You stated that the test is performed on the registered substance ("Phosflex 51B"), but also that the "*Chemical identity of test substance [is] not reported*". ECHA notes that you did not provide any specific details on the test material used in the study in the technical dossier.

The use of existing data on human health properties, from experiments not carried out according to GLP or the test methods referred to in Article 13(3), is considered valid so long as the conditions of Annex XI, section 1.1.2 are met. This study does not have adequate and reliable coverage of the key parameters foreseen to be investigated in the OECD TG 479 or the requested OECD TG 473 or 487. More, specifically (1) the identification data (if known), physical nature and purity of the test material are not provided (2) at least duplicate cultures should be used for each experimental point, and there were not replicates in this experiment. You also stated that there is no data on results from range finding/ screening studies.
In addition, there is not adequate and reliable documentation because you have not provided tabulation of the results, rationale for the dose selection, nor historical negative (solvent/ vehicle) and positive control data (with e.g. ranges, means and standard deviations). ECHA concludes that the conditions of Annex XI, section 1.1.2 are not met, and consequently this study does not provide the information required by Annex VIII, Section 8.4.2.

The technical dossier does not contain any other adaptation in accordance with column 2 of Annex VIII Section 8.4.2. or with the general rules of Annex XI for this standard information requirement.

Therefore 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 chromosome aberration test (test method OECD TG 473) and the *in vitro* mammalian cell micronucleus test (OECD TG 487) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.2. of the REACH Regulation.

In your comments to the draft decision you underlined that test substance used is Phosflex 51B which is the commercial name of the substance EC# 700-990-0. However, ECHA considers that the test material is not the substance subject to this decision. Further, you express the intention to address the requests in this decision by further developing a read across adaptation based on a worst-case approach linked to the presence of triphenyl

phosphate which is present at comparatively much lower amounts in the (proposed target) substance subject to this decision compared to the proposed source (EC 700-990-0). ECHA observes that the you did not provide any read-across hypothesis which addresses the requested information or documentation according to the general rules of Annex XI, section 1.5. The documentation that you provided in your comments does not contain any specific justification whereby relevant human health properties of the registered substance may be predicted from data for the source substances nor have you provided data which would support your worst-case approach. 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. Moreover, ECHA notes that this study does not have adequate and reliable coverage of the key parameters foreseen to be investigated in the OECD TG 479, or the requested OECD TG 473 or 487. In addition, there is no adequate and reliable documentation. For your complete information, ECHA points out that OECD TG 479 was deleted in April 2014 by the OECD council and that according to the ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.7.3.1., Table R.7.7-2.) the OECD TG 479 is not a preferred *in vitro* method for use.

ECHA concludes that the provided study does not provide the information required by Annex VIII, Section 8.4.2.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian chromosome aberration test (test method: OECD TG 473) or *in vitro* mammalian cell micronucleus study (test method: OECD TG 487).

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

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.

ECHA notes that the registration dossier does not contain appropriate study records for this endpoint. Adequate information *on in vitro* gene mutation in mammalian cells will however need to be present in the technical dossier for the registered substance to meet this information requirement provided that both studies requested under 1 and 2 have negative results.

In the technical dossier you have provided a study record for (i) an *in vitro gene* mutation study in mammalian cells (TK locus in L5178Y mouse lymphoma cells), using a guideline "equivalent or similar to OECD TG 476" ([redacted] 1979; key study and reliability score of 2); and (ii) an *in vitro* gene mutation study in mammalian cells (TK locus in L5178Y mouse lymphoma cells) using a guideline "equivalent or similar to OECD TG 476" ([redacted] 1978; key study and reliability score of 2).

ECHA notes that none of the 2 studies were performed according to GLP, and that, for study (i), you stated that the test is performed on the registered substance ("Phosflex 51B"), but also that the "*Chemical identity of test substance [is] not reported*". ECHA notes that you did not provide any specific details on the test material used in both studies.

The use of existing data on human health properties, from experiments not carried out according to GLP or the test methods referred to in Article 13(3), is considered valid so long as the conditions of Annex XI, section 1.1.2 are met. These studies do not have adequate and reliable coverage of the key parameters foreseen to be investigated in the OECD TG 476, specifically (1) the identification data, stability, physical nature and purity of the test material are not provided provided in the technical dossier, (2) at least duplicate cultures should be used for each experimental point, and there were not replicates in this experiment, (3) number of cells plated, treated.
In addition, there is not adequate and reliable documentation because you have not provided tabulation of the results, nor historical negative (solvent/ vehicle) and positive control data (with e.g. ranges, means and standard deviations). ECHA concludes that the conditions of Annex XI, section 1.1.2 are not met, and consequently these studies do not provide the information required by Annex VIII, Section 8.4.3.

The technical dossier does not contain any other adaptation in accordance with column 2 of Annex VIII, Section 8.4.3. or with the general rules of Annex XI for this standard information requirement.

Therefore, 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.

In your comments to the draft decision you underlined that the identity of the test material Phoslfex 51B is clearly referring to the substance EC# 700-990-0. However, ECHA considers that the test material is not the substance subject to this decision. Further, you express the intention to address the requests in this decision by further developing a read across adaptation based on a worst-case approach linked to the presence of triphenyl phosphate which is present at comparatively much lower amounts in the (proposed target) substance subject to this decision compared to the proposed source (EC 700-990-0). ECHA observes that the you did not provide any read-across hypothesis which addresses the request or documentation according to the general rules of Annex XI, section 1.5. The documentation that you provided in your comments does not contain any specific justification whereby relevant human health properties of the registered substance may be predicted from data for the source substances nor have you provided data which would support your worst-case approach. 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. Moreover, as already explained above, these studies do not have adequate and reliable coverage of the key parameters foreseen to be investigated in the OECD TG 476 nor is there adequate and reliable documentation. ECHA concludes that these studies do not provide the information required by 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 both studies requested under 1. and 2. have negative results.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier, you have provided a total of 6 endpoint study records for the repeated dose toxicity endpoint. These include two sub-chronic (90-day) dietary studies and one subacute (28 day) study by the oral route, one 90 day study by the inhalation route, and two 21-day studies by the dermal route. These studies are assessed below:

1) A sub-chronic (90-day) dietary toxicity study with Phosflex 51B in rats, with a guideline "equivalent or similar to OECD TG 408" ([redacted] 1981). The study (key study, reliability score of 2) was not conducted according to the GLP. The concentration of the individual constituents of the test material is within the concentration range of the registered substance as reported in IUCLID section 1.2, with the exception of one: triphenyl phosphate whose concentration is significantly higher than the concentration range reported in IUCLID section 1.2 (1-2.5%).

The use of existing data on human health properties, from experiments not carried out according to GLP or the test methods referred to in Article 13(3), is considered valid so long as the conditions of Annex XI, section 1.1.2 are met. This study does not have adequate and reliable coverage of the key parameters foreseen to be investigated in the OECD TG 408, specifically (1) some organs/ tissues specified in the Guideline document were not examined in histopathology (skin, female mammary gland, spinal cord, bone marrow and peripheral nerve), (2) some required examinations were not performed (ophthalmological examination, blood clotting time, glucose, urea, and creatinine), (3) the dose levels used are not compliant with the Guideline requirement: "*[U]nless limited by the physical-chemical nature or biological effects of the test substance, the highest dose level should be chosen with the aim to induce toxicity but not death or severe suffering.*" You stated that there was "*a biologically significant increase in liver and adrenal weights in the high-dose group, [which] was not regarded as an adverse effect. [...] [A] NOAEL of 107.5 and 124.8 mg/kg bw/day (equivalent to 1600 ppm) was established for males and females, respectively.*"

Although you stated that the "*dose selection is based on the data from a 28-day Dietary Range-Finding Study with Phosflex 51B in Rats (T-10430)*", you did not provide any results of the dose-range finding study and subsequently there is no adequate rationale for dose level selection. Therefore, you have not shown that the highest dose level was chosen with

the aim to induce toxicity, and so this is a key parameter of the Test Guideline which is not covered.

For all the above, ECHA concludes that the conditions of Annex XI, section 1.1.2 are not met, and consequently this study does not provide the information required by Annex IX, Section 8.6.2.

Finally ECHA notes, from the sub-chronic (90-day) dietary toxicity study ,the following effects which lead to specific concerns about neurotoxicity: the cholinesterase activity was significantly decreased in both males and females in red blood cell, plasma and brain, and the clinical chemistry findings were affected by the treatment (eg. decrease in LDH in both males and females, increase in sodium levels in males and decrease in sodium levels in females, ...). You reported that the cholinesterase activity was generally not dose-dependent except for plasma cholinesterase activity decrease in females. Also the absolute liver weight was significantly increased for male and female high dose animals. An indication for a dose-related response was found, especially in males. The absolute adrenal weight was significantly increased for females of the high dose group only. Relative liver weight was significantly increased for males and females of the high dose group and males of the mid-dose group. Relative kidney weight was significantly increased for males of the high dose group only, with an indication for a dose-dependent response. The same accounted for relative adrenal weight in the high dose females. These effects were not considered toxicologically relevant in absence of changes in blood chemistry.

2) A 90-day dietary repeated dose toxicity study conducted with a guideline "equivalent or similar to OECD TG 408", not conducted according to the GLP ([redacted] 1974; reliability score of 2). You stated that the "Name of test material (as cited in study report) is t-butylphenyl diphenyl phosphate" (EC number 260-391-0) and you also indicated as a constituent of the test material "Reaction mass of t-butylphenyldiphenyl phosphate and bis-t-butylphenylphenyl phosphate and triphenyl phosphate". No further information is available on the composition of the test material.

ECHA considers that the test material is not the registered substance, and that you have sought to adapt the information requirement according to Annex XI, section 1.5. However as you did not provide any read-across hypothesis or documentation, the adaptation does not meet the requirements of Annex XI, section 1.5. Therefore your adaptation is rejected.

This study does not have adequate and reliable coverage of the key parameters addressed in the OECD TG 408 (as required by Annex XI, 1.5), specifically (1) some required examinations/ measurements were not performed (blood clotting time, sodium, potassium, creatinine and cholesterol, total protein and albumin), (2) the dose levels used are not compliant with the Guideline requirement: "*[U]nless limited by the physical-chemical nature or biological effects of the test substance, the highest dose level should be chosen with the aim to induce toxicity but not death or severe suffering.*" You stated that "*[N]one of the examinations performed revealed any adverse effects related to test article treatment in any of the dosage groups.*"

You did not provide an alternative rationale for the selection of the doses used. Therefore, you have not shown that the highest dose level was chosen with the aim to induce toxicity, and so this is an additional key parameter of OECD TG 408 which is not covered. Finally the limited reporting does not allow ECHA to make an independent assessment of the study, and so this is a failure to provide adequate and reliable documentation, as required by Annex XI, 1.5.

ECHA concludes that the conditions of Annex XI, section 1.5 are not met for all the above reasons, and consequently this study does not provide valid information required by Annex IX, Section 8.6.2.

3) A one-month study performed with a guideline "equivalent or similar to OECD TG 407", using dietary administration of the test material "Santicizer 154, tert-butyl phenyl diphenyl phosphate", not according to GLP ([redacted] 1981). The concentration of the major constituent, triphenyl phosphate ([redacted]%), is significantly higher than in the registered substance (1-2.5%) and therefore is considered not to represent the concentration range of the registered substance as reported in IUCLID section 1.2.

ECHA considers that the test material is not the registered substance, and that you have sought to adapt the information requirement according to Annex XI, Section 1.5. However as you did not provide any read-across hypothesis or documentation, the adaptation does not meet the requirements of Annex XI, section 1.5. Therefore your adaptation is rejected.

Additionally, this study does not cover an exposure duration comparable to or longer than the OECD TG 408, specifically the exposure duration is less than 90 days. This study does not have adequate and reliable coverage of the key parameters addressed in OECD TG 408, specifically the number of animals per dose group is significantly lower than in the 90 day sub-chronic toxicity study. Therefore, the sensitivity of a 28-day study is much lower than that of a 90-day study.

ECHA concludes that also these conditions of Annex XI, section 1.5 are not met, and consequently this study does not provide valid information which can be used to meet the information requirement of Annex IX, Section 8.6.2..

4) A 90-day repeated dose toxicity study, via the inhalation route, using a guideline "equivalent or similar to OECD TG 413", not according to GLP ([redacted] 1979). Firstly, ECHA considers that aerosol inhalation is not an appropriate route of administration according to Annex IX, section 8.6.2, column 2. More specifically, you have not demonstrated that exposure of humans via inhalation is likely taking into account the vapour pressure of the substance and/or the possibility of exposure to aerosols, particles or droplets of an inhalable size. Secondly, according to Annex IX, 8.6.2, column 1, the oral route is the most appropriate route of administration since (i) the oral route is both the default and preferred route, (ii) there is no indication of inhalation specific toxicity or concern, and (iii) the oral administration will likely lead to higher systemic availability of the substance. Consequently, ECHA concludes that studies by the inhalation route do not meet the information requirement.

The use of existing data on human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) is valid so long as the conditions of Annex XI, section 1.1.2 are met. This study does not have adequate and reliable coverage of the key parameters foreseen to be investigated in the OECD TG 408, specifically (1) one dose level was omitted which is not compliant with the OECD TG 413, (2) the dose levels used are not compliant with the Guideline requirement *"[T]he high concentration level should result in a clear level of toxicity but not cause lethality or persistent signs that might lead to lethality or prevent a meaningful evaluation of the results."* You stated that *"no clear test article- or dose-related effects were observed in rats"*. You considered that the top dose of 100 mg/m^3 (approximately equivalent to

28,75 mg/ kg/ bw oral dose) was a NOAEC, although you did note a significantly higher relative liver weight in males compared to controls. You have therefore failed to meet the OECD TG 413 criteria for clear level of toxicity, and there is no other explanation provided for the dose selection for this study. Finally there is no indication that a concentration of up to 2mg/L (2000 mg/m^3) could not be achieved, as per paragraph 13 of GD 39/ OECD TG 413: *"For particles aerosol testing > 2 mg/L should only be attempted if a respirable particle size can be maintained/ achieved (refer to GD 39)."* Therefore, you have not shown that the highest dose level was chosen with the aim to induce toxicity, and so this is an incompliance with the OECD TG 413.

ECHA concludes that you have failed to meet the requirements of Annex XI, section 1.1.2, and consequently this study does not provide reliable information which can be used to meet the information requirement of Annex IX, Section 8.6.2..

5) A three-week dermal toxicity study, performed on rabbits (10 animals per dose group; [redacted] 1979), using a guideline "equivalent or similar to OECD guideline 410", not performed according to GLP. You stated that the test is performed on the registered substance. Nonetheless ECHA notes that you did not provide any specific details on the composition of the test material used in the study.

Firstly, ECHA considers that dermal exposure is not an appropriate route of administration according to Annex IX, section 8.6.2, column 2. More specifically, you have not demonstrated that exposure of humans via dermal route is likely. Secondly, according to Annex IX, 8.6.2, column 1, the oral route is the most appropriate route of administration since (i) the oral route is both the default and preferred route, (ii) there is no indication of inhalation specific toxicity or concern, and (iii) the oral administration will likely lead to higher systemic availability of the substance. Consequently, ECHA concludes that studies by the dermal route do not meet the information requirement.

The use of existing data on human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) is valid so long as the conditions of Annex XI, section 1.1.2 are met. This study does not have adequate and reliable coverage of the key parameters foreseen to be investigated in the OECD TG 408, specifically (1) the exposure duration is less than 90 days and the number of animals per dose group is significantly lower than in the 90 day sub-chronic toxicity study. Therefore, the sensitivity of a 28-day study is much lower than that of a 90-day study. Also since exposure duration is a relevant parameter, ECHA concludes that the conditions of Annex XI, section 1.1.2 are not met. Thus this study does not provide valid information which can be used to meet the information requirement of Annex IX, 8.6.2.

The study was performed with a dose concentration of 10, 100, and 1000 mg/kg. The No-Observed-Adverse-Effect-Concentration was reported as 10 mg/kg/bw, because of a significant dose-response depression of terminal cholinesterase in the treated males and females, in the mid and high dose groups. The results suggest that the substance may cause some neurotoxicity in rabbits, because the *"mean terminal cholinesterase values (RBC and brain) were depressed compared to control in a dose-related pattern (significant in mid and high dose); mean plasma cholinesterase values of low-dose males and females were comparable to control values"*.

6) A 21-day repeated dose toxicity study using a test guideline "equivalent or similar to OECD TG 410", using only two dose levels, with 10 animals per sex per dose ([redacted]

1976), not performed according to GLP. No information is available on the composition of the test material.

Firstly, ECHA considers that dermal exposure is not an appropriate route of administration according to Annex IX, section 8.6.2, column 2. More specifically, you have not demonstrated that exposure of humans via dermal route is likely. Secondly, according to Annex IX, 8.6.2, column 1, the oral route is the most appropriate route of administration since (i) the oral route is both the default and preferred route, (ii) there is no indication of inhalation specific toxicity or concern, and (iii) the oral administration will likely lead to higher systemic availability of the substance. Consequently, ECHA concludes that studies by the dermal route do not meet the information requirement.

The use of existing data on human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) is valid so long as the conditions of Annex XI, section 1.1.2 are met. This study does not have adequate and reliable coverage of the key parameters foreseen to be investigated in the OECD TG 408, specifically (1) one dose level was omitted which is not compliant with the OECD TG 410, (2) the exposure duration is less than 90 days and the number of animals per dose group is significantly lower than in the 90 day sub-chronic toxicity study. Therefore, the sensitivity of a 28-day study is much lower than that of a 90-day study. Also since exposure duration is a relevant parameter, ECHA concludes that the conditions of Annex XI, section 1.1.2 are not met. Thus this study does not provide valid information which can be used to meet the information requirement of Annex IX, 8.6.2.

The Lowest-Observed-Adverse-Effect-Level was 100 mg/ kg/ bw due to "*significant treatment-related depression in the mean terminal cholinesterase values (plasma, erythrocyte and brain) compared to control*".
Similarly to study 5 above, the results may indicate the potential of the substance to cause some neurotoxicity.

To conclude, for the several grounds explained above, none of the studies presented above provide the information required to meet the requirement set in Annex IX, Section 8.6.2.. Consequently, there is no adequate information present in the dossier.

The technical dossier does not contain any other adaptation in accordance with column 2 of Annex IX, Section 8.6.2. or with the general rules of Annex XI for this standard information requirement.

Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report (substance is liquid with low vapour pressure of 0,01 Pa at 20°C), ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 5.0, December 2016) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, even though the information indicates that human exposure to the registered substance by the inhalation or dermal route is possible (PROCs 7, 10, 11, 13), they also indicate a concern for systemic toxicity (liver toxicity/ neurotoxicity) that requires further information on repeated dose toxicity by the oral route.

Hence, the test shall be performed by the oral route using the test method OECD TG 408. According to the test method OECD TG 408, the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Furthermore, as described above, ECHA considers that there are indications of an effect for which the available evidence is inadequate for toxicological and/or risk characterisation, specifically that the registered substance may be neurotoxic. Hence this potential for neurotoxicity should be further investigated with the registered substance, as per Annex IX, Section 8.6.2., Column 2.

The test method EU B.43./OECD TG 424 "*has been designed to obtain the information necessary to confirm or to further characterise the potential neurotoxicity of chemicals in adult animals. It can either be combined with existing Test Guidelines for repeated dose toxicity studies or be carried out as a separate study" (paragraph 3).* OECD TG 424 is also designed to "*detect major neurobehavioral and neuropathological effects in adult rodents. [...] Any changes observed should be evaluated in conjunction with correlative histopathological, haematological or biochemical data as well as data on other types of systemic toxicity" (paragraph 8).*

However, ECHA notes that to fulfil the standard information requirement in the registration dossier for repeated dose toxicity, as set out in Annex IX, Section 8.6.2., it is also necessary to provide comprehensive information on other organ systems in addition to the nervous system, and so you shall include additional examinations/parameters as established in test method OECD TG 408 on sub-chronic toxicity (90-day) study.

Hence, the neurotoxicity study in rodents (EU B.43./OECD TG 424) shall be combined with the repeated dose 90-day oral toxicity study (OECD TG 408) so as to include the following additional examinations and parameters to the proposed study:

- a range-finding study may be performed to aid in the determination of the doses to be used;
- the laboratory performing the study should present data demonstrating its capability to carry out the OECD TG 424 study and the sensitivity of the procedures used, including recommended observations;
- the minimum numbers of animals to be used per group is set out in OECD TG 424, Table 1, under the column of "*neurotoxicity study conducted as: combined study with the 90-day study*" (minimum of 15 males and 15 females);
- organ weights and organ/body weight ratios, haematological examinations, clinical biochemistry determinations and gross necropsy should be performed so as to fulfil the criteria set out in both the OECD TG 408 and OECD TG 424; and
- histopathological examinations should be performed so as to fulfil the criteria set out in both the OECD TG 408 and OECD TG 424.

In your comments to the draft decision you provided further information on the test material Phosflex 51B, that was used in (1) the sub-chronic (90-day) dietary toxicity study ([redacted] 1981) which represents substance EC# 700-990-0. With respect to (2) the 90-day dietary repeated dose toxicity study ([redacted] 1974), you underlined that test material EC number 260-391-0 refers to the EC#700-990-0 substance before it was split on a request of ECHA and that, as there is no further description of the material in the report, we must assume it resembles EC#700-990-0. Concerning (3) the one-month study ([redacted] 1981), you underlined that the test material relates to Santicizer 154. ECHA notes that the

concentration of TPP (triphenyl phosphate) is outside the concentration ranges of this constituent as reported in the substance identity profile of the registered substance and of substance EC# 700-990-0.

ECHA considers that the test materials used in these aforementioned studies do not represent the substance subject to this decision. Further, you express the intention to address the requests in this decision by further developing a read across adaptation based on a worst-case approach linked to the presence of triphenyl phosphate which is present at comparatively much lower amounts in the (proposed target) substance subject to this decision compared to the proposed source(s) (EC 700-990-0). ECHA observes that the you did not provide any read-across hypothesis which addresses the request or documentation according to the general rules of Annex XI, section 1.5. The documentation that you provided in your comments does not contain a specific justification whereby relevant human health properties of the registered substance may be predicted from data for the source substances nor have you provided data which would support your worst-case approach. 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 or which address the identified concerns. Further, as already stated in the decision, none of the studies either individually or taken together provide adequate and reliable adequate and reliable coverage of the key parameters addressed in the OECD TG 408 and hence it does not provide valid information required by Annex IX, Section 8.6.2.

Finally, in your comments you indicated you have intention not to further address the dermal and inhalation studies.

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: Neurotoxicity study in rodents (test method: EU B.43./OECD TG 424) combined with the Sub-chronic toxicity study (90-day) in rats, oral route (test method: OECD TG 408), as specified above in this section.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "pre-natal developmental toxicity study" (test method 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.

In the technical dossier you have provided a study record for a:

1) A "pilot teratology study"was performed in rats, by gavage ([redacted] 1980). The study was done according to GLP, from GD6 to GD19 and the test material was administered, unchanged, at doses of 250, 500, 1000, 2500, and 5000 mg/ kg/ bw. You stated that the test was equivalent or similar to OECD Guideline 414, and also that *"[s]tudy was not performed according to a guideline..."*. The test material is described as "Reaction mass of t-

butylphenyldiphenyl phosphate and bis-t-butylphenylphenyl phosphate and triphenyl phosphate", but you did not provide any further information on the composition of the test material tested.

The use of existing data on human health properties from experiments not carried out according to the test methods referred to in Article 13(3) is valid so long as the conditions of Annex XI, section 1.1.2 are met. This study does not have adequate and reliable coverage of the key parameters foreseen to be investigated in the OECD TG 414 because fewer animals (only 5 females) were used per dose group as compared to the Guideline requirement (20 per group). Therefore, the sensitivity of pilot study is much lower than that a prenatal developmental study. ECHA concludes that the conditions of Annex XI, section 1.1.2 are not met. Thus this study does not provide valid information which can be used to meet the information requirement of Annex IX, 8.7.2.

2) A pre-natal developmental toxicity study using the OECD TG 414, was performed in rats, with no deviations, and according to GLP ([redacted] 1981). The study was conducted at doses of 300, 1000, and 3000 mg/ kg/ bw administered unchanged by gavage, from GD6 to GD19.
The test material is described as "Reaction mass of t-butylphenyldiphenyl phosphate and bis-t-butylphenylphenyl phosphate and triphenyl phosphate". No further information is available on the composition of the test material.
ECHA considers that the test material is not the registered substance, and that you have sought to adapt the information requirement according to Annex XI, section 1.5. However as you did not provide any read-across hypothesis or documentation, the adaptation does not meet the requirements of Annex XI, section 1.5. Therefore your adaptation is rejected.

3) A pre-natal developmental toxicity study using a guideline "equivalent or similar to" OECD TG 414, was performed in rats, not according to GLP, on the substance Phosflex 51B ([redacted] 1982). The concentration of the individual constituents of the test material is within the concentration range of the registered substance as reported in IUCLID section 1.2, with the exception of one: triphenyl phosphate whose concentration is significantly higher than the concentration range reported in IUCLID section 1.2 (1-2.5%).

The use of existing data on human health properties from experiments not carried out according to the test methods referred to in Article 13(3) is valid so long as the conditions of Annex XI, section 1.1.2 are met. According to the summary in the technical dossier, this study does not have adequate and reliable coverage of the key parameters foreseen to be investigated in the OECD TG 414 because fewer animals (only 7 females) were used per dose group as compared to the Guideline requirement (20 per group). Therefore, the sensitivity of such study is much lower than that a prenatal developmental study. ECHA concludes that the conditions of Annex XI, section 1.1.2 are not met and therefore this study does not provide adequate information which can be used to meet the information requirement of Annex IX, 8.7.2.

4) A waiver for the 2nd species pre-natal developmental toxicity study, with the justification that "a *developmental toxicity study in a second species can be waived because in the Guidance Document on Information Requirements and Chemical Safety Assessment Chapter R.7a: Endpoint specific guidance is indicated that the study does not need to performed, as the developmental toxicity study in rats does not indicate the substance to cause developmental effects, and there are no indications that the substance may be reproductive*

toxic in the 90-day repeated dose toxicity studies." This is not a valid adaptation for a prenatal developmental toxicity study in a first species.
The technical dossier does not contain any other adaptation in accordance with column 2 of Annex IX, Section 8.7.2. or with the general rules of Annex XI for this standard information requirement.

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

In your comments to the draft decision you underlined that the test material in (1) the pilot teratology study ([redacted] 1980) is the same as in the full study. Concerning (2) the pre-natal developmental toxicity study using the OECD TG 414 ([redacted] 1981), you indicated that the test material "Sancticizer 154" relates to substance EC#700-990-0. With respect to (3) the pre-natal developmental toxicity study ([redacted] 1982), you indicated that the test material, Phosflex 51B, has a composition that falls within the concentration ranges of substance EC# 700-990-0. However, ECHA considers that the test material used in these aforementioned studies do not represent the substance subject to this decision. Further, you express the intention to address the requests in this decision by developing a read across adaptation based on a worst-case approach linked to the presence of triphenyl phosphate which is present at comparatively much lower amounts in the (proposed target) substance subject to this decision compared to the proposed source(s) (EC 700-990-0). ECHA observes that the you did not provide any read-across hypothesis which addresses the request or provide documentation according to the general rules of Annex XI, section 1.5. The documentation that you provided in your comments does not contain any specific justification whereby relevant human health properties of the registered substance may be predicted from data for the source substances nor have you provided data which would support your worst-case approach. 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 substances.

With respect to (3) the pre-natal developmental toxicity study ([redacted] 1982), ECHA assessed the full study report, provided as Attachments 8a+b to your comments, and agrees that the number of animals per dose group is in line with the Guideline requirement (20 per group) and that the key parameters are extensively listed in the full report. Therefore, ECHA concludes that this study provides adequate and reliable information in respect concerning the tested material which differs significantly from the registered substance subject to this decision. Hence, for the reasons outlined above, it does not provide information to meet the requirements of Annex IX in respect of the substance subject to the decision.

According to the test method 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 liquid, 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: OECD TG 414) in a first species (rabbit or rat]) by the oral route.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex IX, Section 9.1.5., column 2. You provided the following justification for the adaptation *"According to Column 2 of Annex IX, long-term toxicity testing shall be proposed in case the chemical safety assessment performed according to Annex I indicates a need for further testing. As the substance is not classified, no exposure and risk assessment has been performed and therefore further testing is not triggered, nor deemed necessary."*

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.5., column 2 because ECHA considers that there is a need to further investigate the effects on aquatic organisms.

You assume that lack of effects in the available short term tests is sufficient to conclude that further testing is not needed. ECHA notes that the measured solubility value of the substance is 122ug/L. According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) poorly water soluble substances have a water solubility below 1 mg/L or below the detection limit of the analytical method of the test substance. Accordingly ECHA notes that the registered substance is poorly soluble.

ECHA considers that substances that are poorly soluble in water require a longer time to be significantly taken up by the test organisms and so steady state conditions are likely not to be reached within the duration of a short-term toxicity test. For this reason, short-term tests may not give a true measure of toxicity for such substances and toxicity may actually not even occur at the water solubility limit of the substance if the test duration is too short. For such substances long-term aquatic testing is required to accurately assess the risks to the aquatic environment.

ECHA concludes that that given the poor solubility of the substance the available short term tests are unreliable and the absence of toxicity in these short term tests is irrelevant. As there are no reliable short-term studies available on aquatic invertebrates or on fish for the registered substance, the Integrated testing strategy (ITS) outlined in ECHA Guidance on information requirements and chemical safety assessment (version 4.0, June 2017), Chapter R7b (Section R.7.8.5 including Figure R.7.8-4) is not applicable in this case and

long-term studies on both invertebrates and fish are required.

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

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint. According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) *Daphnia magna* reproduction test (test method EU C.20. / OECD TG 211) is the preferred test to cover the standard information requirement of Annex IX, Section 9.1.5.

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: Daphnia magna reproduction test (test method: EU C.20./OECD TG 211).

Notes for your consideration

Once results of the test on long-term toxicity to aquatic invertebrates are available, you shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation.

Due to the low solubility of the substance in water you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

In addition, regarding the use of the Water Accommodated Fraction (WAF) approach, please note that the WAF approach is problematic when used with a test substance containing several constituents, as in the case of the registered substance. In such cases the toxicity cannot be allocated to specific constituents directly and interpretation of the results in the risk assessment requires careful consideration taking into account differences in fate of the constituents in the environment. When constituents of varying solubility are present there can be partitioning effects which limit dissolution in the water. These effects should be minimised and appropriate loadings selected accordingly to allow an appropriate determination of the toxicity of the different constituents. In that respect, it is critical that a robust chemical analysis is carried out to identify those constituents present in the water to which the test organisms are exposed. Additionally, chemical analysis to demonstrate attainment of equilibrium in WAF preparation and stability during the conduct of the test is required. Methods capable of identifying gross changes in the composition of WAFs with time are required such as ultra-violet spectroscopy or total peak area have been used successfully for this purpose. The method used to prepare the WAF should be fully described in the test report and evidence of its compositional stability over time should be provided.

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

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Long-term toxicity testing on fish" is a standard information requirement as laid down in Annex IX, Section 9.1.6. of the REACH Regulation. Adequate information on Fish, early-life stage (FELS) toxicity test (Annex IX, 9.1.6.1.), or Fish, short-term toxicity test on embryo and sac-fry stages (Annex IX, 9.1.6.2.), or Fish, juvenile growth test (Annex IX, 9.1.6.3.) needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement according to Annex IX, Section 9.1.6., column 2. You provided the following justification for the adaptation *"According to Column 2 of Annex IX, long-term toxicity testing shall be proposed in case the chemical safety assessment performed according to Annex I indicates a need for further testing. As the substance is not classified, no exposure and risk assessment has been performed and therefore further testing is not triggered, nor deemed necessary."*

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.5., column 2 because ECHA considers that there is a need to further investigate the effects on aquatic organisms.

For the reasons already explained in Section 6 or this decision ECHA concludes that the registered substance is poorly soluble and consequently long-term aquatic testing is required to accurately assess the risks to the aquatic environment.

ECHA concludes that that given the poor solubility of the substance the available short term tests are unreliable and the absence of toxicity in these short term tests is irrelevant. As there are no reliable short-term studies available on aquatic invertebrates or on fish for the registered substance, the Integrated testing strategy (ITS) outlined in ECHA Guidance on information requirements and chemical safety assessment (version 4.0, June 2017), Chapter R7b (Section R.7.8.5 including Figure R.7.8-4) is not applicable in this case and long-term studies on both invertebrates and fish are required.

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

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

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) fish early-life stage (FELS) toxicity test (test method OECD TG 210), fish short-term toxicity test on embryo and sac-fry stages (test method EU C.15. / OECD TG 212) and fish juvenile growth test (test method EU C.14. / OECD TG 215) are the preferred tests to cover the standard information requirement of Annex IX, Section 9.1.6.

However, the FELS toxicity test according to OECD TG 210 is more sensitive than the fish, short-term toxicity test on embryo and sac-fry stages (test method EU C.15 / OECD TG 212), or the fish, juvenile growth test (test method EU C.14. / OECD TG 215), as it covers several life stages of the fish from the newly fertilized egg, through hatch to early stages of growth (see ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), *Chapter R7b, Figure R.7.8-4).*

Moreover, the FELS toxicity test is preferable for examining the potential toxic effects of substances which are expected to cause effects over a longer exposure period, or which require a longer exposure period of time to reach steady state (ECHA *Guidance Chapter R7b,* version 4.0, June 2017).

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: Fish, early-life stage (FELS) toxicity test (test method: OECD TG 210).

Notes for your consideration

Once results of the test on long-term toxicity to fish are available, you shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation.

ECHA notes that due to lack of effects in short-term studies it is not possible to determine the sensitivity of species. Therefore, the Integrated testing strategy (ITS) outlined in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b (Section R.7.8.5 including Figure R.7.8-4), is not applicable in this case and the long-term studies on both invertebrates and fish are requested to be conducted.

Due to the low solubility of the substance in water you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

In addition, regarding the use of the Water Accommodated Fraction (WAF) approach, please note that the WAF approach is problematic when used with a test substance containing several constituents, as in the case of the registered substance. In such cases the toxicity cannot be allocated to specific constituents directly and interpretation of the results in the risk assessment requires careful consideration taking into account differences in fate of the constituents in the environment. When constituents of varying solubility are present there can be partitioning effects which limit dissolution in the water. These effects should be minimised and appropriate loadings selected accordingly to allow an appropriate determination of the toxicity of the different constituents. In that respect, it is critical that a robust chemical analysis is carried out to identify those constituents present in the water to which the test organisms are exposed. Additionally, chemical analysis to demonstrate attainment of equilibrium in WAF preparation and stability during the conduct of the test is required. Methods capable of identifying gross changes in the composition of WAFs with time are required such as ultra-violet spectroscopy or total peak area have been used successfully for this purpose. The method used to prepare the WAF should be fully described in the test report and evidence of its compositional stability over time should be provided.

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 13 September 2017.

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

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

ECHA took into account your comments and did not amend the requests.

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.