ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 10 December 2018

Addressee: [redacted]

Decision number: CCH-D-2114448639-34-01/F
Substance name: Reaction mass of benzyl 2-ethylhexyl adipate and bis(2-ethylhexyl) adipate and dibenzyl adipate
List number: 905-983-8
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 20/12/2016
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) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102 with the registered substance;**

2. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: OECD TG 408) in rats modified to include urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy; with the registered substance;**

3. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2., column 2; test method: OECD TG 414) in a second species (rabbit) oral route with the registered substance;**

4. **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;**

5. **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 ;**

6. **Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: CO2 evolution test, OECD TG 301B) or**

   Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: Closed bottle test, OECD TG 301D) or

Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: Manometric respirometry test, OECD TG 301F) or

Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: Ready biodegradability – CO2 in sealed vessels (headspace test), OECD TG 310) 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 ***17 December 2020***. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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

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.)

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

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

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

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

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.

You have provided a test from the year 1991 according to OECD TG 471 and GLP with an assigned reliability score of 1. The test used four different strains of S. typhimurium TA 1535, TA 1537, 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 current guidelines, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation.

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

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

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

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

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

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.

You have not provided any study record of a sub-chronic toxicity study (90 day) in the dossier that would meet the information requirement of Annex IX, Section 8.6.2.

a) Information provided

You have sought to adapt this information requirement according to Annex XI, Section 1.2., weight of evidence. Hence, ECHA has evaluated your adaptation with respect to this provision.

You have not provided an explanation or justification on how the sources of information/studies, which you have provided enable an assumption or conclusion that the registered substance does or does not have a dangerous property with respect to sub-chronic toxicity study (90 day). ECHA understands that you conclude that the registered substance does not have a dangerous (hazardous) property with respect to repeated dose toxicity.

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

i. [redacted] 2013, reliability score of 1, a 28-d study in rat according to OECD 407 and GLP compliant. Doses used: 0, 100, 300, 1000 mg/kg bw/day for 30 days to 5 + 5 animals. Urinalysis, not examined. In the liver, a minimal centrilobular hepatocellular hypertrophy was observed in males starting at 300 mg/kg bw/day. At 1000 mg/kg bw/day, the change corroborated the minimally higher mean liver weight recorded, and a macroscopically swollen liver noted in one animal. This minor liver change was considered to indicate a metabolic adaptation of the liver due to induction of hepatic microsomal enzymes and not as an adverse effect. In the kidney of males multifocal minimally dilated cortical and medullary tubules was seen at histopathology starting at 300 mg/kg bw/day. They were associated mainly at 1000 mg/kg bw/day, with multifocal minimal or mild cortical tubular degeneration. In addition, an increased incidence and severity of renal hyaline droplets in corticotubular cells in males was noted, considered to represent α2-microglobulin and which were observed starting at 100 mg/kg bw/day. The occurrence of α2-microglobulin was considered to be a male rat-specific event without toxicological relevance for humans. NOAEL female 1000 mg/kg bw/d, NOAEL male could not be established (LOAEL 100 mg/kg bw/d).

ii. Bornmann, 1956, publication, reliability score of 2, no test guideline and no GLP indicated, and limited information given for the 1-year oral study. Groups of ca. 17 three months old male and female rats received twice weekly 0.5 or 1.0 mL/kg bw of a 50% solution of 'Reaction mass of benzyl 2-ethylhexyl adipate and bis(2-ethylhexyl) adipate and dibenzyl adipate' in oleum olivarum DAB 6 over a period of 1 year which was followed by a post treatment observation period of 3 months

iii. Bornmann, 1956, publication, reliability score of 2, no test guideline indicated, no GLP compliance, admin. twice weekly for 6 weeks. 15 young male rats received twice weekly per gavage 1.0 mL/kg bw of a 50 % solution of the registered substance in oleum olivarum DAB 6 over a period of 6 weeks. 15 male control rats received oleum olivarum DAB 6 only. Before and during treatment time oxygen consumption was measured. After the treatment period of 6 weeks animals were examined histopathologically.

iv. Bornmann, 1956, publication, reliability score of 2, no test guideline indicated, no GLP compliance, administration once daily for 6 weeks. Dose: 1ml/kg bw. 15 young female rats received daily per gavage 1.0 mL/kg bw of a 50 % solution of the registered substance in oleum olivarum DAB 6 over a period of 6 weeks. 15 female control rats received oleum olivarum DAB 6 only. An Allen-Doisy test was performed. Before and during treatment time oxygen consumption was measured. After the treatment period of 6 weeks animals were examined histopathologically.

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

An adaptation pursuant to Annex XI, Section 1.2. requires sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property with respect to the information requirement in question including an adequate and reliable documentation while the information from each single source alone is regarded insufficient to support this notion.

Your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance with respect to a sub-chronic toxicity study (OECD TG 408). Relevant elements are in particular exposure route, duration and dose levels, two genders, sensitivity and depth of investigations to detect specific organ toxicity.

ECHA has analysed the sources of information provided and notes the following deficiencies:

i. In the technical dossier you have provided a study record for a "repeated dose 28-day oral toxicity study" (2013) (test method: OECD TG 407). However, this study does not provide the information required by Annex IX, Section 8.6.2., because 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 (OECD TG 408). Therefore, the sensitivity of a 28-day study is much lower than that of a 90-day study.

ii. The publication (1956) that is provided is a non-guideline, non GLP one-year study and is not an adequate study since the rats were dosed twice weekly and only two doses were used. According to the test guideline (OECD TG 408) the animals should be dosed daily and three dose levels should be used. Hence the data provided by this study cannot be considered as being equivalent to the data generated from the corresponding test method OECD TG 408 as there is no adequate and reliable coverage of the key parameters foreseen to be investigated in OECD TG 408 (Annex

XI, Section 1.1.2. (2)).

iii. Similarly in the six week study (1956) non-guideline, non-GLP, there is only one dose tested and the frequency of treatment was twice weekly. In addition, and as explained above, the exposure duration is less than 90 days and only males were investigated. Hence the data provided by this study cannot be considered as being equivalent to the data generated from the corresponding test method OECD TG 408 as there is no adequate and reliable coverage of the key parameters foreseen to be investigated in OECD TG 408 and the exposure duration is less than 90-days, as required by OECD TG 408 (Annex XI, Section 1.1.2. (2) and (3)).

iv. Finally, you refer to a publication (1956, non-guideline, non GLP) with a six-week study with only one dose level used. According to the test guideline (OECD TG 408) at least three doses should be used. In addition, the exposure duration is less than 90 days and only females were investigated. Hence the data provided by this study cannot be considered as being equivalent to the data generated from the corresponding test method OECD TG 408 as there is no adequate and reliable coverage of the key parameters foreseen to be investigated in OECD TG 408 (Annex XI, Section 1.1.2. (2) and (3)).

As indicated above, essential information on key parameters, such as number of doses, frequency of treatment and exposure duration, is missing. As a consequence ECHA cannot assess the potential hazard regarding this particular endpoint.

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

Therefore, the general rules for adaptation laid down in Annex XI, Section 1.2. of the REACH Regulation are not met and your adaptation of the information requirement is rejected.

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

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance is a liquid of very low vapour pressure. According to the uses reported in the chemical safety report there are industrial and professional spray applications (PROCs 7 and 11) and consumer uses (coatings, sealants and adhesives, paints/remover and thinners). Even though this information might indicate that human exposure to the registered substance by the inhalation route is likely, there are effects reported in the available oral acute and sub-acute repeated dose toxicity studies (OECD TG 407) that indicate a concern for systemic toxicity 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.

In the 28-day repeated dose toxicity study (OECD TG 407) present in your registration dossier, adverse effects, multifocal minimally dilated cortical and medullary tubules was seen at histopathology starting at 300 mg/kg bw/day and increased incidence and severity of renal hyaline droplets in corticotubular cells in males were observed in the kidneys of male rats and not in female rats. The fact that these effects were only observed in male rats may indicate that the registered substance may induce alpha-2u-globulin-mediated nephropathy. ECHA accordingly considers that the kidney is a target organ of the registered substance. Since humans do not excrete alpha-2u-globulin and this mode of action is considered not relevant to humans the involvement of alpha-2u-globulin in the kidney effects is a key parameter for establishing the relevance of the kidney effects for risk assessment. For these reasons, ECHA considers that urinalysis is required to investigate kidney function (which is an option provided for in paragraphs 3, 4, and 37 of OECD TG 408). Additionally, a full histopathological examination (paragraphs 3, 4, 45 and 47 of OECD TG 408), which is to include immunohistochemical investigation of renal pathology to determine if the pathology is indeed mediated by alpha-2u globulin.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Repeated dose 90-day oral toxicity study (test method: OECD TG 408) in rats modified to include urinalysis and a full histopathological examination which is to include immunohistochemical investigation of renal pathology to determine if the pathology is mediated by alpha-2u globulin nephropathy.

3. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2., column 2) in a second species

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. Annex IX, Section 8.7.2., column 2 provides that the decision on the need to perform a pre-natal developmental toxicity study on a second species at a tonnage level of 100 to 1000 tonnes per year should be based on the outcome of the first test and all other relevant and available data. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet these information requirements.

The technical dossier contains a pre-natal developmental toxicity study with rats by the oral route. This study fulfils the standard information requirement for a pre-natal developmental toxicity study in a first species (Annex IX, Section 8.7.2.).

However, with reference to Annex IX, Section 8.7., column 2, ECHA sees a need to request a pre-natal developmental toxicity study with a second species. According to the ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.6.2.3.2 (version 6.0, July 2017), a study on the second species is necessary since the pre-natal developmental toxicity study, with the rat species, shows pre-natal developmental toxicity.

ECHA has reviewed the findings from the study (OECD TG 414; GLP compliant) by [redacted] (2016) and notes the following fetal skeletal findings:

i. A dose-dependent increase was noted in the fetuses examined for the metacarpal (not ossified): in the mid and high dose groups (500 and 1000 mg/kg bw/day, respectively), there was a statistically significant increase (+11.9% and +40.6%, respectively), when compared to the control group.
ii. Also a dose-dependent decrease was noted in the fetuses examined for the

ossified forepaw phalanges. In the mid and high dose groups there was a statistically significant decrease (-10.5% and -26.1%, respectively), when compared to the control group.

iii. At the high dose group, when compared to the control group, there was also a statistically significant increase in the incomplete ossification for interparietal (+19.4%), femur (+15.9%) and occipital (+11.8%).

ECHA also notes that according to the study (2016) there were no treatment related effects for maternal toxicity and the highest dose of 1000 mg/kg bw/day was established as the NOAEL threshold level. Hence, the skeletal effects noted in this study might be an indication of developmental toxicity.

ECHA furthermore notes that you intend tol conduct a reproduction/developmental toxicity screening test according to OECD TG 421. You provide the following justification: *"The study will be conducted to finally conclude on the relevance of the observed delayed ossifications in fetuses dosed with the limit dose of 1000 mg/kg bw/day in a recent developmental toxicity study".* However, ECHA notes that the screening study does not provide information on increased incidences in external, skeletal and soft tissue malformations and variations in foetuses. Additionally, the screening study is performed on only ten mating pairs while in a pre-natal developmental toxicity study 20 pregnant females per dose group are required. Hence the screening study cannot address the concerns noted in the first species pre-natal developmental toxicity study. An appropriate study to clarify the concern based on the outcome of the first study is a prenatal developmental toxicity study in a second species (non-rodent).

The observed effects noted in the first species pre-natal developmental toxicity study (2016) are not sufficient for the substance to meet the classification criteria to Category 1B, but they cause further concern for pre-natal developmental toxicity. Thus, another pre-natal developmental toxicity study on the second species is needed for a comprehensive evaluation of pre-natal developmental toxicity, including determination of the classification category.

Hence, 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.

The test in the first species was carried out with rats. According to the test method EU OECD TG 414, the rat is the preferred rodent species and the rabbit is the preferred non-rodent species. On the basis of this default assumption, ECHA considers that the test should be performed with rabbit as a second 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 second species (rabbit) by the oral route.

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4. 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 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 REACH Annex IX, long-term testing shall be proposed by the registrant if the Chemical Safety Assessment indicates the need to investigate further the effects on aquatic organisms. Acute toxicity studies for all three trophic levels of aquatic organisms are available for the registered substance 'Reaction mass of benzyl 2-ethylhexyl adipate and bis(2-ethylhexyl) adipate and dibenzyl adipate'. Neither in the short-term fish test, the short-term daphnia test nor the algae test adverse effects could be observed within the tested concentration range. As further no direct or indirect entry of the registered substance 'Reaction mass of benzyl 2-ethylhexyl adipate and bis(2-ethylhexyl) adipate and dibenzyl adipate' into the environment is expected and due to a very low BCF, indicating no potential for bioaccumulation, the investigation of further long-term tests seems to be unjustified. On the basis of the present data the registered substance 'Reaction mass of benzyl 2-ethylhexyl adipate and bis(2-ethylhexyl) adipate and dibenzyl adipate' does not have to be classified and therefore no hazard to any compartment, including the environment, is expected."

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.5., column 2 because 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 ranges from < 0.068 to 0.844 mg/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 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. Methods 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.

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

"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 REACH Annex IX, long-term testing shall be proposed by the registrant if the Chemical Safety Assessment indicates the need to investigate further the effects on aquatic organisms. Acute toxicity studies for all three trophic levels of aquatic organisms are available for the registered substance 'Reaction mass of benzyl 2-ethylhexyl adipate and bis(2-ethylhexyl) adipate and dibenzyl adipate'. Neither in the short-term fish test, the short-term daphnia test nor the algae test adverse effects could be observed within the tested concentration range. As further no direct or indirect entry of the registered substance 'Reaction mass of benzyl 2-ethylhexyl adipate and bis(2-ethylhexyl) adipate and dibenzyl adipate' into the environment is expected and due to a very low BCF, indicating no potential for bioaccumulation, the investigation of further long-term tests seems to be unjustified. On the basis of the present data the registered substance 'Reaction mass of benzyl 2-ethylhexyl adipate and bis(2-ethylhexyl) adipate and dibenzyl adipate' does not have to be classified and therefore no hazard to any compartment, including the environment, is expected."

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.6., 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 ranges from < 0.068 0.844 mg/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) 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) can be performed 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, Section R.7.8.4.1.*
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

Before conducting any of the tests mentioned above in points 4 and 5 you shall consult the ECHA *Guidance on information requirements and chemical safety assessment (*version 4.0, June 2017*)*, Chapter R7b, Section R.7.8.5 to determine the sequence in which the aquatic long-term toxicity tests are to be conducted and the necessity to conduct long-term toxicity testing on fish.

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. As the registered substance has a reported low water solubility and is adsorptive to highly adsorptive, long-term studies are indicated.

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 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. Methods 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.

6. Ready biodegradability (Annex VII, Section 9.2.1.1.)

"Ready biodegradability" is a standard information requirement as laid down in Annex VII, section 9.2.1.1. 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.

In the technical dossier you have provided a study record for an OECD TG 301 C study (1989, GLP, reliability 2). However, this study does not provide the information required by Annex VII, Section 9.2.1.1., because it is not considered as reliable for the following reasons.

Firstly, a robust study summary is not provided. According to Articles 10(a)(vii) and Sections 1.1.4 and 3.1.5 of Annex I to the REACH Regulation, a technical dossier shall include robust study summaries of all key data used in the human health and environmental hazard assessment. Article 3(28) defines a robust study summary as a *"detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study minimising the need to consult the full study report."* ECHA considers that the level of information reported for this study is not sufficient to allow an independent assessment. There are insufficient experimental details (T°C and pH not reported) and the degradation curve is not provided. Also, critically, it is not clear from the provided information if the validity criteria of the OECD TG 301C study are met.

You reported for your reference substance that no biodegradation occurred after 6 days and that biodegation reached 69% after 12 days. OECD TG 301C specifies that percentage of biodegradation should be at least 40% after 7 days and 65% after 14 days. If these conditions are not met, the test should be repeated. Based on information provided in your study summary, it is not clear whether the percentage degradation of the reference substance reached 40% in 7 days as required and consequently ECHA does not consider the study to be reliable.

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.

Regarding the test method, depending on the substance profile, you may conclude on ready biodegradability, by applying the most appropriate and suitable test guideline among those listed in the ECHA Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017) and in the paragraph below. The test guidelines include the description of their applicability domain.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to perform one of the following tests with the registered substance subject to the present decision:

Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: CO2 evolution test, OECD TG 301B)

or

Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: Closed bottle test, OECD TG 301D)

or

Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: Manometric respirometry test, OECD TG 301F)

or

Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: Ready biodegradability – CO2 in sealed vessels (headspace test), OECD TG 310) with the registered substance

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 17 January 2018.

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.

In your comments you agreed to the draft decision. ECHA took your comments into account 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 carrying out the tests required by the present decision, it is important to ensure that the particular sample of substance tested 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. If the registration of the substance covers different grades, the sample used for the new tests must be suitable to assess these.

   Furthermore, 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.