EUROPEAN CHEMICALS AGENCY

Helsinki, 24 October 2017

Addressee: [redacted]

Decision number: CCH-D-2114375349-37-01/F
Substance name: 4,4'-Isopropylidenediphenol, oligomeric reaction products with 1-chloro-2,3-epoxypropane, esters with acrylic acid
EC number: 500-130-2
CAS number: 55818-57-0
Registration number: [redacted]
Submission number: [redacted]
Submission date: 17.03.2016
Registered tonnage band: 1000+T

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. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) in Wistar rats, oral route with the registered substance specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce some toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;**
   - **Cohorts 2A and 2B (Developmental neurotoxicity); and**
   - **Cohort 3 (Developmental immunotoxicity).**
2. **Identification of degradation products (Annex IX, Section 9.2.3.) using appropriate test method;**
3. **Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.) test method: Daphnia magna reproduction test, EU C.20, OECD 211;**
4. **Long-term toxicity testing on fish (Annex IX, Section [9.1.6.1. / 9.1.6.2. / 9.1.6.3]) test method: Fish, early-life stage (FELS) toxicity test, OECD TGD 210;**

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

You are required to submit the requested information in an updated registration dossier by **31 October 2019**. You shall also 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. Advice and further observations are provided in Appendix 3.

Appeal

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

Authorised[1] by Kevin Pollard, Head of Unit, Evaluation E1

[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

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

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

The basic test design of an extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X.

If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in the ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 6.0, July 2017) which is further referred to as "ECHA Guidance R.7.6.".

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

a) The information requirement

In the technical dossier of IUCLID section 7.8.1., you have provided the following:

- Key study: "*screening for reproductive/developmental toxicity*" in Crl:CD (SD) rats (OECD TG 422; GLP; oral gavage), [redacted] 2010 (study report), Rel.1, NOAEL>900 mg/kg bw/day for the reproductive/developmental toxicity screening test.

- Justification to omit extended one-generation reproductive toxicity study: "*In a recent GLP combined repeated dose and reproduction / developmental screening test conducted according to OECD guideline 422, no signs of toxicity to reproduction that could be attributable to the test item were identified on male and female rats exposed by gavage up to 900 mg/kg bw/day from 2 weeks before mating. Moreover no foetal malformations were observed in the OECD 414 performed on rat. Due to the absence of adverse effects on fertility and foetal developmental in the available studies, no further reproduction testing is needed*".

In addition, you have provided in the IUCLID section of 7.8.2., the following:

- Key study: "developmental toxicity" in Wistar rat (OECD TG 414, GLP, oral gavage), [redacted] 2015 (study report), Rel.1, NOAEL 1000 mg/kg bw/day for developmental toxicity.

While you have not explicitly claimed an adaptation, you have provided justification that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2., weight of evidence. Hence, ECHA has evaluated your provided information with respect to this provision.

ECHA notes that you have not provided a conclusion for the weight of evidence adaptation. ECHA understands that you conclude implicitly that the registered substance does not have a dangerous property with respect to reproductive toxicity.

ECHA has evaluated your weight of evidence information according to REACH Annex XI, Section 1.2., and has assessed whether you have provided "*sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that the substance has or has not a particular dangerous property*" with respect to the information requirement of Annex X, Section 8.7.3., columns 1 and 2 for an extended one-generation reproductive toxicity study. ECHA has further evaluated the information according to ECHA *Guidance on information requirements and chemical safety assessment* R.4.4. (version 1.1, December 2011) by considering whether the criteria given in that guidance, *i.e.* relevance, reliability and adequacy for the purpose, apply to the information you have provided. ECHA also considered the number of animals used in the studies provided and the consistency in the effects presented across the lines of information. ECHA came to a view on whether the set of information presented addresses the properties of the substance by covering, as a minimum, the most relevant elements investigated in an extended one-generation reproductive toxicity study (EU B.56./OECD TG 443) with adequate sensitivity and depth of investigation to detect reproductive toxicity.

ECHA considers that the extended one-generation reproductive toxicity study provides relevant information on two aspects, namely on sexual function and fertility in parental P0 and F1 generation (further referred to as 'sexual function and fertility') and on toxicity observable after birth until adulthood in F1 generation (further referred to as 'toxicity in offspring'). Relevant elements for 'sexual function and fertility' are in particular functional fertility (oestrous cycle, sperm parameters, mating behaviour, conception, pregnancy, parturition, and lactation) in the P0 parental generation after sufficient pre-mating exposure and histopathological examinations of reproductive organs in both P and F1 generations. Relevant elements for 'toxicity in offspring' are in particular peri- and post-natal investigations of the F1 generation up to adulthood, investigations on developmental neurotoxicity, and investigations on developmental immunotoxicity.

With respect to the aspect of 'sexual function and fertility' of P and F1 generation, you have provided information on histopathological changes in major reproductive organs and information on oestrous cycle, mating behaviour, conception, pregnancy, parturition and lactation (OECD TG 422 screening study). The information from prenatal developmental toxicity study in rats (OECD TG 414) is limited to maintenance of pregnancy from implantation up to close to the parturition (from gestation day 6 to 20) showing no effects up to dose level of 1000 mg/kg bw/day.

However, ECHA notes that the statistical power (sensitivity) and depth of investigations to detect reproductive toxicity is lower in OECD TG 422 than that of the extended one-generation reproductive toxicity study, and certain investigations are not included, such as histopathology of the reproductive organs in F1 animals in adulthood, precoital interval, thyroid hormone and oestrous cycle measurements in F1 animals. Furthermore, you did not provide information on sperm parameters in P and F1 generations.
With respect to the aspect of 'toxicity in offspring' observable after birth until adulthood, you have provided very limited reliable information. More specifically, the prenatal developmental toxicity study (OECD TG 414) investigates only pre-natal developmental toxicity and the OECD TG 422 screening study investigates developmental toxicity only until postnatal day 4. An extended one-generation reproductive toxicity study provides extensive information on developmental toxicity observable during pre- and postnatal period until adulthood. This information includes growth, survival/mortality, certain external malformations, investigations related to hormonal modes of action (anogenital distance, nipple retention, thyroid hormone measurements) and sexual maturation (vaginal opening, perpetual separation, time to first oestrous cycle in F1 generation) and histopathology of gonads and sex organs in F1 animals in adulthood.

Furthermore, the criteria to include investigations for developmental neurotoxicity and developmental immunotoxicity are fulfilled as explained below. However, you have not provide any information in regards to these endpoints.

Hence, you did not provide enough reliable information to support your assumption/ conclusion that the substance does not have a dangerous (hazardous) property with respect to sexual function and fertility and offspring toxicity regarding to main elements of reproductive toxicity as specified in extended one-generation reproductive toxicity study, including investigations for developmental neurotoxicity and developmental immunotoxicity properties of the registered substance.

Hence, ECHA considers that the individual sources of information you provided, do not allow to assume/conclude that the substance does not have a particular dangerous property with respect to the information requirement for Annex X, Section 8.7.3.

In your comments on the draft decision according to Article 50(1) of the REACH Regulation you have concluded that "*All above considerations demonstrate that that there is no oral exposure potential, that inhalative exposure is almost null and anyway purely theoretical due to non detected vapours, and that systemic exposure by dermal route is almost null due to prevention of skin sensitisation and negligible dermal absorption potential. In the absence of any relevant systemic exposure potential in real use conditions, further investigating systemic effects (OECD 443) would not lead to any benefit for human health. It would therefore not be a justified use of Vertebrate animal lives*.

Waving of the OECD 433 study is therefore claimed in reference to disposition in REACH Annex XI:

- *Point 1.2 Testing not scientifically necessary, using the weight-of-evidence provided above;*
- *Point 3.2 (a) – Exposure-based waving, non-SCC: we meet the conditions of §(a)(i) and § (a) (iii), and with regard to § (a) (ii), the current long-term systemic DNELs are highly reliable as several robust studies on systemic effects are available by oral route (OECD 408, OECD 422, OECD 414).*
- *In addition, management, procedures and handling practice at manufacturing and downstream user sites can be compared with strictly controlled conditions, due to the sensitising properties and highly reactivity (risk of polymerisation) of the monomers used in this specific market sector. We are therefore close to conditions in point 3.2 (b) – Exposure-based waving, SCC.*
- *In all cases we also meet the conditions of point 3.3 as the conditions of use are communicated through the supply chain via the extended safety data sheet".*

ECHA already explained above why the general rules for adaptation laid down in Annex XI, Section 1.2. of the REACH Regulation are not met.

Your comments on exposure based adaptation moreover do not fulfil the three cumulative conditions for omission of the testing according to REACH Annex XI, Section 3.2.(a), which are:

(i) the results of the exposure assessment covering all relevant exposures throughout the life cycle of the substance demonstrate the absence of or no significant exposure in all scenarios of the manufacture and all identified uses as referred to in Annex VI section 3.5;

(ii) a DNEL or a PNEC can be derived from results of available test data for the substance concerned taking full account of the increased uncertainty resulting from the omission of the information requirement, and that DNEL or PNEC is relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes [Footnote: For the purpose of subparagraph 3.2(a)(ii), without prejudice to column 2 of Section 8.7 of Annexes IX and X, a DNEL derived from a screening test for reproductive/developmental toxicity shall not be considered appropriate to omit a prenatal developmental toxicity study or a two-generation reproductive toxicity study. For the purpose of subparagraph 3.2(a)(ii), without prejudice to column 2 of section 8.6 of Annexes IX and X, a DNEL derived from a 28-day repeated dose toxicity study shall not be considered appropriate to omit a 90-day repeated dose toxicity study.];

(iii) the comparison of the derived DNEL or PNEC with the results of the exposure assessment shows that exposures are always well below the derived DNEL or PNEC.

While you have provided a justification as to why the first criterion is met in your opinion, ECHA notes that whether the residual exposure is significant or not cannot be assessed as conditions (ii) and (iii) are not met.

The second criterion requires that the DNEL shall be "*relevant and appropriate both to the information requirement for be omitted and for risk assessment purposes*". Furthermore, the footnote to the second criterion in section 3.2.(a)-(ii) states that "*without prejudice to column 2 of Section 8.7 of Annexes IX and X, a DNEL derived from a screening test for reproductive/developmental toxicity shall not be considered appropriate to omit a prenatal developmental toxicity study or a two-generation reproductive toxicity study*".

However, you have used the OECD TG 422 screening study ([redacted], 2010) to derive the DNEL for reproductive toxicity. As explained above, the DNEL derived from an OECD TG 422 screening study cannot be used to adapt the information requirement of a two-generation reproductive toxicity study or an extended-one generation reproductive toxicity study. Therefore, the criterion set out in Annex XI, Section 3.2.(ii) is not met and the adaptation possibility of Annex XI, Section 3.2. cannot be applied to this case.
With regard to the third criterion, section 3.2.(a)(iii), ECHA notes that you have not demonstrated that the criterion is met.

In addition, you have considered the risk management measures in place due to the sensitising property of the substance and concluded that you are "*close to the conditions of the general rules for adaptation according to REACH Annex XI, Section 3.2.(b)*". However, you have not demonstrated that the strictly controlled conditions as set in Article 18(4) (a) to (f) do indeed apply for all relevant scenarios throughout the life cycle of the registered substance. In contrary, as you admit in your comments, there is "almost null", *i.e.* residual, exposure. Consequently, ECHA considers that the general rules of adaptation according to REACH Annex XI, Section 3.2.(b) are not met.

Therefore, ECHA concludes that the general rules for adaptation laid down in Annex XI, Section 1.2., and Annex XI, Section 3.2.(a) and (b) of the REACH Regulation are not met and your adaptation of the information requirement is rejected.

b) The specifications for the study design

Premating exposure duration and dose-level setting

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

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA Guidance R.7.6.

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

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

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity as described in column 2 of 8.7.3., Annex X. When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.

ECHA notes that existing information on the registered substance itself derived from an available *in vivo* study, 90-day oral toxicity study according to OECD TG 408 ([redacted], 2015), shows evidence of reduced locomotor activity at all dose levels in males suggesting a neuro-behavioural effect, which you have indicated in your report as "*test item-related*". This effect becomes statistically significant at the highest dose level.

ECHA concludes that the developmental neurotoxicity Cohorts 2A and 2B need to be conducted because there is a particular concern on (developmental) neurotoxicity based on the results from the above-identified *in vivo* study [redacted], 2015).

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity as described in column 2 of 8.7.3., Annex X.

ECHA notes that existing information on the registered substance itself derived from an available *in vivo study*, 90-day oral toxicity study according to OECD TG 408 ([redacted] 2015), shows evidence of effects related to immunotoxicity at 1000 mg/kg bw/day without significant general toxicity. Increased neutrophil, monocyte counts, and decreased lymphocytes in the mesenteric lymph nodes were noted in both sexes, and lower lymphocyte counts were observed in males. In addition, globulin levels were reduced in males and the thymus weight (absolute, and relative to the brain and body weight) was reduced in females.

Furthermore the registered substance has classification for skin sensitisation (Skin Sens. 1B), which supports the concern for developmental immunotoxicity.

ECHA concludes that the developmental immunotoxicity Cohort 3 needs to be conducted because there is a particular concern on (developmental) immunotoxicity based on the results from the above-identified *in vivo* study ([redacted], 2015).

The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

Species and route selection

According to the test method EU B.56./OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA Guidance R.7.6, chapter 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.

Further specifications of the study

ECHA notes that in the 90 day toxicity study ([redacted], 2015) effects on the reproductive organs of male Wistar rats were observed (reduced sperm motility and prostate weights at all dose levels). While such effects were not observed in the OECD TG 422 screening study ([redacted], 2015) that investigated Crl:CD(SD) rats.

Hence, ECHA considers that Wistar rats might be more sensitive than the Crl:CD(SD) rats with respect to reproductive toxicity. Therefore, the extended one-generation reproductive toxicity study shall be performed with Wistar rats.

b) Outcome

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method EU B.56./OECD TG 443), in Wistar rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation;
- Cohorts 2A and 2B (Developmental neurotoxicity); and
- Cohort 3 (Developmental immunotoxicity).

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. However, you may expand the study by including the extension of Cohort 1B, if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the new information shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA Guidance R.7.6.

You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented. The study design must be justified in the dossier and, thus, the existence/non-existence of the conditions/triggers must be documented.

2. Identification of degradation products (Annex IX, Section 9.2.3.)

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

The identification of the degradation products is a standard information requirement according to column 1, Section 9.2.3. of Annex IX 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. Column 2 of Section 9.2. of Annex IX indicates that the study needs to be conducted if the chemical safety assessment (CSA) according to Annex I indicates the need to investigate further the degradation of the substance and its degradation products and that the choice of the appropriate test(s), which may include simulation degradation tests in appropriate media, depends of the results of the CSA.

According to Annex IX, Section 9.2.3., column 2 of the REACH Regulation, identification of degradation products is not needed if the substance is readily biodegradable. ECHA notes that based on the information in the technical dossier, the registered substance is not readily biodegradable (*see:* results from the OECD 301F study).

Furthermore, ECHA notes that you have not provided any justification in your chemical safety assessment (CSA) or in the technical dossier for why there is no need to provide information on the degradation products

Pursuant to Annex XIII of the REACH Regulation "the identification [of PBT and vPvB substances] shall also take account of the PBT/vPvB-properties of relevant constituents of a substance and relevant transformation and/or degradation products". Your CSA does not contain any information on the degradation products and on whether they could be PBT/vPvB or not.

Information on degradation products shall also be taken into account for the exposure assessment (Annex I 5.2.4. of the REACH Regulation) and for the hazard assessment (e.g. column 2 of Annex X 9.4 and Annex X 9.5.1 of the REACH Regulation). Finally, information on degradation products is required for the preparation of Section 12 of the safety datasheet (Annex II of the REACH Regulation).

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.
The aerobic mineralisation in surface water – simulation biodegradation (test method EU C.25. / OECD TG 309) is an appropriate test method to obtain information on the primary degradation and the formation of major transformation products in water. The analytical methods used for the identification of the degradation products will have to be substance-specific. When analytically possible, identification, stability, behaviour, molar quantity of metabolites relative to the parent compound should be evaluated. In addition, degradation half-life, log Kow and potential toxicity of those metabolites may be investigated. As specified in the OECD 309 test guideline, higher concentrations of the test substance (e.g., >100 µg/L) and a test temperature within the frame provided by the study guideline could be used to overcome potential analytical limitations for the identification and quantification of major transformation products.

According to Annex XIII of REACH, the identification of PBT/vPvB substances shall take account of the PBT/vPvB-properties of relevant constituents of the substance. Section R.11.4.1 of REACH Guidance document R.11 on PBT/vPvB assessment (version 3.0, June 2017) further indicates that "constituents, impurities and additives should normally be considered relevant for the PBT/vPvB assessment when they are present in concentration of ≥ 0.1% (w/w). This limit of 0.1% (w/w) is set based on a well-established practice recognised in European Union legislation". Therefore degradation products should be identified for each constituents, impurities and additives present in the registered substance in concentrations at or above 0.1% (w/w) or, if not technically feasible, in concentrations as low as technically detectable.

In your comments to the draft decision you state that "*Therefore, these substances being not PBT or vPvB, no further investigation on the biodegradation of the test substance to assess its persistency are needed nor the identification of degradation products.*" ECHA acknowledges that the registered substance is not B. Nevertheless, for the reasons stated above, this does not release you from the need to identify the degradation products and assess their PBT/vPvB-properties.

Therefore, pursuant to Article 41(1)(a) and(b) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Identification of the degradation products (Annex IX, Section 9.2.3.) by using an appropriate and suitable test method, as explained above in this section.

3. 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., column 2.

You provided the following justification for the adaptation: "*In accordance with column 2 of REACH Annex IX, the study shall be proposed if the chemical safety assessment according to Annex I indicates the need to investigate further the effects on aquatic organisms. As the exposure assessment does not indicate the need to investigate further the effects on aquatic organisms (as all the RCR`s to all the compartments are below 1 and all the supported uses are therefore assessed to be safe, no further long-term testing is proposed for aquatic compartment.*"

The test presented in your dossier for the determination of the water solubility of your substance shows that the water solubility depends on the initial concentration of the substance: a water solubility of 82 mg/L was derived when 5 g of substance was added to 1L of water, whereas a water solubility of 484 mg/L was found when 50 g of substance was added to 1L of water. Your dossier further indicates that the preliminary test estimated the water solubility to be < 8 mg/L. You have acknowledged that your substance "*consists of a mixture of compounds of different molecular weights. Each constituent contributes to a different degree to overall solubility, depending on its own individual solubility and its mass fraction in the test item. Thus, analytical results depend on the proportions of Bisphenol A-Epoxy-diacrylat and water used in the experiment*". Furthermore, in the robust study summaries for the short-term toxicity test on *Daphnia* and for the toxicity test on algae it is indicated that "*the test item was not well soluble in test water*". Therefore, based on the information provided in your dossier, ECHA considers that some constituents of your substance are likely to be poorly soluble.

Poorly soluble substances require 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 poorly water soluble substances and toxicity may actually not even occur at the water solubility limit of the substance if the test duration is too short. Still, long-term toxicity cannot be excluded and should be investigated. Annex VIII 9.1.3. and Annex VII 9.1.1. of the REACH Regulation explicitly recommend that long-term aquatic toxicity tests be considered if the substance is poorly water soluble.

ECHA considers that the available information in your chemical safety assessment does not rule out long-term effects to aquatic organisms and that further long-term effects on aquatic organisms need to be investigated. Consequently ECHA concludes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.5., column 2 and 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.

In your comments to the draft decision you agree to perform this test.

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).

4. 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 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., column 2.

You provided the following justification for the adaptation: "*In accordance with column 2 of REACH Annex IX, the study shall be proposed if the chemical safety assessment according to Annex I indicates the need to investigate further the effects on aquatic organisms. As the exposure assessment does not indicate the need to investigate further the effects on aquatic organisms (as all the RCR`s to all the compartments are below 1 and all the supported uses are therefore assessed to be safe, no further long-term testing is proposed for aquatic compartment.*"

The test presented in your dossier for the determination of the water solubility of your substance shows that the water solubility depends on the initial concentration of the substance: a water solubility of 82 mg/L was derived when 5 g of substance was added to 1L of water, whereas a water solubility of 484 mg/L was found when 50 g of substance was added to 1L of water. Your dossier further indicates that the preliminary test estimated the water solubility to be < 8 mg/L. You have acknowledged that your substance "*consists of a mixture of compounds of different molecular weights.*

Each constituent contributes to a different degree to overall solubility, depending on its own individual solubility and its mass fraction in the test item. Thus, analytical results depend on the proportions of Bisphenol A-Epoxy-diacrylat and water used in the experiment".
Furthermore, in the robust study summaries for the short-term toxicity test on *Daphnia* and for the toxicity test on algae it is indicated that "*the test item was not well soluble in test water*". Therefore, based on the information provided in your dossier, ECHA considers that some constituents of your substance are likely to be poorly soluble.

Poorly soluble substances require 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 poorly soluble substances and toxicity may actually not even occur at the water solubility limit of the substance if the test duration is too short. Still, long-term toxicity cannot be excluded and should be investigated. Annex VIII 9.1.3. and Annex VII 9.1.1. of the REACH Regulation explicitly recommend that long-term aquatic toxicity tests be considered if the substance is poorly water soluble.

ECHA considers that the available information in your chemical safety assessment does not rule out long-term effects to aquatic organisms and that further long-term effects on aquatic organisms need to be investigated. Consequently ECHA concludes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 9.1.6., column 2 and 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.

The following test methods can cover the standard information requirement of Annex IX, Section 9.1.6. for long-term toxicity testing on fish: fish early-life stage (FELS) toxicity test (Annex IX, section 9.1.6.1. of the REACH Regulation), fish short-term toxicity test on embryo and sac-fry stages (Annex IX, section 9.1.6.2. of the REACH Regulation) and fish juvenile growth test (Annex IX, section 9.1.6.3. of the REACH Regulation). ECHA considers that the FELS toxicity test (Annex IX, section 9.1.6.1. of the REACH Regulation) is more appropriate than the fish, short-term toxicity test on embryo and sac-fry stages, or than the fish, juvenile growth test, as it covers several life stages of the fish from the newly fertilised egg, through hatch to early stages of growth. Moreover, the FELS toxicity test is preferable for examining the potential toxic effects of substances which are expected to cause effects under a longer-term exposure, or which require a longer period of time to reach steady state (for example for those substance with a high log Kow). The revised OECD test guideline 210 (adopted on 26 July 2013) is a suitable test method for addressing the information requirements of Annex IX, section 9.1.6.1. of the REACH Regulation.

In your comments to the draft decision you "*propose to follow an integrated testing strategy (ITS) as recommended in section R.7.8.5., Chapter R.7b of the ECHA Guidance on information requirements and chemical safety assessment (version 3.0, February 2016) by performing first a long-term toxicity test on aquatic invertebrate. (...)If no PNEC can be derived or if the chemical safety assessment reports a risk with the PNEC derived based on the results obtained in the long-term toxicity testing on aquatic invertebrates, a Long-term toxicity testing on fish (OECD TG 210) will be proposed.*" (...) *In addition, due to null releases to water in all local contributing scenarios (and very low release also in the widespread professional use), it is already possible now to predict that a Long-term toxicity testing on fish (OECD 210) is not needed from a CSA perspective.*"

ECHA notes that Member State Competent Authorities submitted Proposals for Amendment (PfAs) where they also considered that the aquatic ITS may be applicable in this case and that further advice on possible alternative for animal testing should be provided in the decision. Based on the PfA ECHA further clarified why the aquatic ITS is not applicable in this case and updated the note for consideration for possible alternatives for animal testing.

In your comments on the PfAs you state that "*chronic toxicity data are necessary due to the fact that exposure is not ensured in an appropriate time-frame in short-term toxicity studies, due to the aforementioned poor water solubility of certain constituents of the substance*". Nevertheless you agree with the MSCAs PfA that a step-by-step process starting with the long-term aquatic invertebrate study could be applied. You consider that the "*low water solubility issue could be properly addressed with a long-term daphnia study*" and following that study it could be decided whether the long-term fish study would be need in addition.

ECHA acknowledges your agreement that due to the low water solubility of some of the constituents the registered substance, a UVCB, can be considered a low water solubility substance as also discussed by ECHA in the paragraphs above in this section. Furthermore, you agree that short-term aquatic tests do not provide a true measure of the toxic potential of low water solubility substances as already discussed by ECHA in the paragraphs above.

ECHA notes that for the derivation of the $PNEC_{aquatic}$ data on three trophic levels, on aquatic invertebrates, fish and aquatic plants, is required (ECHA Guidance on information requirements and chemical safety assessment, v.4.0, June 2017, Chapter R7b, Section R.7.8.5.3). As discussed above, the short-term data is not applicable in this case, long-term data on all three trophic levels is needed for the derivation of $PNEC_{aquatic}$ and to perform the chemical safety assessment.

Furthermore, ECHA notes that due to the low water solubility the short-term data cannot serve as a compelling evidence to predict relative differences (or lack of) in species sensitivity required to apply the aquatic ITS (*ECHA Guidance on information requirements and chemical safety assessment*, Chapter R.7b (version 3.0, February 2016), Section R.7.8.5.3.).

ECHA notes further that REACH requires registrants to consider long-term studies when the substance is poorly water soluble (e.g. water solubility below 1 mg/L or below the detection limit of the analytical method of the test substance based on *ECHA Guidance on information requirements and chemical safety assessment*, Chapter R.7b (version 4.0, June 2017), Section R.7.8.5.). Therefore, in this case long-term data is required to accurately assess the effects of the low water solubility registered substance on aquatic organisms.
For the reasons stated above, the aquatic ITS (*ECHA Guidance on information requirements and chemical safety assessment*, Chapter R.7b (version 3.0, February 2016), Section R.7.8.5.3.) is not applicable and it is necessary to provide long-term data on both aquatic invertebrates and on fish.

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 for requests 3 and 4
Before conducting the above test you are advised to consult the ECHA Guidance on information requirements and chemical safety assessment, Chapters R.4 (v.1.1, December 2011), R.5 (v.2.1, December 2011), R.6 (May 2008), R.7b (v 4.0, June 2017) and R.7c (v 3.0, June 2017). If you decide to adapt the testing requested according to the specific rules outlined in Annexes VI to X and/or according to general rules contained in Annex XI of the REACH Regulation, you are referred to the advice provided in practical guides on "How to use alternatives to animal testing to fulfil your information requirements for REACH registration".

As indicated in ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.7.8.2. (version 4.0, June 2017), test guideline OECD 210 does not cover reproductive endpoints and therefore, other test guidelines should be considered for endocrine disrupting chemicals or when other effects not covered by early fish development are expected to be of particular relevance.

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).

Deadline to submit the requested information in this decision

In the draft decision communicated to you the time indicated to provide the requested information was 24 months from the date of adoption of the decision. In your comments on the MSCAs PfAs, you requested an extension of the timeline to 36 months. You considred a longer timeline necessary in case a testing stragtey to aquatic toxiicty testing was appl;ied. ECHA notes that as fully discussed in section 4 above the tiered testing strategy is not applciable in this case, hence ECHA considers it not necessary to extend the deadline. Furthermore you considered deadline extension necessary due to the substance being diffcult to test. However, ECHA notes that due to the human helath related requests in the decision, the timeline provided is already longer than would normally be provided for aquatic tests alone. ECHA hence considers the timeline suffcicient for conducting the auqatic tests requested. Therefore, ECHA has not modified the deadline of the decision.

ECHA
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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 11 August 2016.

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 amended the request(s).

You were notified that the draft decision does not take into account any updates after 15 November 2016. You updated your registration with submission number [redacted] on 7 March 2017 as a reaction to ECHA Decision CCH-D-2114308070-69-01/F. Your comments on the compliance check draft decision and updated dossier information "*Bioaccumulation in fish, aqueous or dietary exposure (Annex IX, Section 9.3.2.; test method: OECD 305)*" fulfilled the information requirement. Given the exceptional circumstances in which requested information from the above mentioned earlier compliance check was due during the decision making of the current compliance check, ECHA has taken into account the above mentioned update when processing this decision, resulting in the removal of the request "*Simulation testing on ultimate degradation in surface water (Annex IX, Section 9.2.1.2.)*".

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

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

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

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-55 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

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

3. In relation to the information required by the present decision, the sample of the substance used for the new test(s) must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance 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 test(s) is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new test(s) must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.