Helsinki, 24 February 2021

Addressees
Registrants of 386-071_CCDFB listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
29/08/2019

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: 1,1'-(1,1,2,2-tetramethylethylene)dibenzene
EC number: 217-568-2
CAS number: 1889-67-4

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed in B.1. and B.2. below by ***31 May 2024*** and all other information listed below by ***30 July 2025***.

Requested information must be generated using the Substance unless otherwise specified.

A. Information required from all the Registrants subject to Annex VII of REACH

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

B. Information required from all the Registrants subject to Annex IX of REACH

1. 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

2. Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.; test method: OECD TG 443) in rats, oral route specified as follows:

   - Ten weeks premating exposure duration for the parental (P0) generation;
   - Dose level setting shall aim to induce systemic toxicity at the highest dose level;
   - Cohort 1A (Reproductive toxicity);
   - Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation which shall be followed to weaning; and
   - Cohorts 2A and 2B (Developmental neurotoxicity).

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

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

4. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.1.; test method OECD TG

210);

5. Simulation testing on ultimate degradation in surface water (Annex IX, Section 9.2.1.2.; test method EU C.25./OECD TG 309) at a temperature of 12 °C;

6. Soil simulation testing (Annex IX, Section 9.2.1.3.; test method EU C.23./OECD TG 307) at a temperature of 12 °C;

7. Sediment simulation testing (Annex IX, Section 9.2.1.4.; test method EU C.24./OECD TG 308) at a temperature of 12 °C;

8. Identification of degradation products (Annex IX, 9.2.3.) using an appropriate test method;

9. Bioaccumulation in aquatic species (Annex IX, Section 9.3.2; test method OECD TG 305).

Reasons for the request(s) are explained in the following appendices:

- Appendices entitled "Reasons to request information required under Annexes VII to IX of REACH", respectively.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

To comply with your information requirements you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

The studies relating to biodegradation and bioaccumulation are necessary for the PBT assessment. However, to determine the testing needed to reach the conclusion on the persistency and bioaccumulation of the Substance you should consider the sequence in which these tests are performed and other conditions described in Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Approved[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

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

Appendix A: Reasons to request information required under Annex VII of REACH

1. Growth inhibition study on aquatic plants (Annex VII, Section 9.1.2.)

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

You have provided a study conducted according to OECD TG 201 with the Substance using different serial dilutions of a supersaturated stock solution.

We have assessed this information and identified the following issue:

Tests on substances must be conducted in accordance with the OECD test guidelines or other internationally recognised test method (Article 13(3) of REACH). OECD TG 201 is the preferred guideline to fulfil this information requirement. The guideline indicates that for difficult to test substances, OECD Guidance 23 is to be followed.

In particular for poorly soluble substances, OECD TG 201 and OECD Guidance 23 provide that, aquatic toxicity tests can be performed using individually prepared supersaturated solutions. However, using different serial dilutions of a supersaturated stock solution is not allowed in OECD Guidance 23 (or in ECHA Guidance R7b) for substances containing several constituents (or impurities).

During the preparation of the supersaturated solution, the proportions of the dissolved constituents and impurities will depend on their individual water solubility and on the mass-to-volume ratio of the preparation. Consequently, the partitioning behaviour and water solubility between the constituents will be different depending on the loading rate used. Using serial dilutions of a single stock of a supersaturated solution would not address properly the toxicity of the different constituents or impurities of the substance with several constituents or impurities. Using individually prepared supersaturated solutions is regarded as a more conservative approach.

According to the data available in your dossier, the Substance is poorly water soluble (water solubility: 0.08 mg/L at 20°C). It is a mono-constituent substance, but it contains some impurities (up to [redacted] of the Substance composition).

For the study you have provided, a supersaturated stock solution which was prepared with a loading rate of 1000 mg/L. Different serial dilutions were used to prepare the different test concentrations. A statistically significant inhibitory effect was observed on the growth of the algae for dilutions corresponding to more than 20% of the initial loading rate of 1000 mg/L. You concluded that the NOEC was between 100 mg/L and 1000 mg/L as nominal loading rate.

As the Substance is poorly water soluble, it can be regarded as difficult to test.

You chose to conduct the study by preparing different serial dilutions of a supersaturated stock solution. However, this approach is not valid under OECD Guidance 23 and ECHA Guidance R7b. You have not justified or demonstrated that the method applied would accurately address the toxicity of the different constituents or impurities of the Substance.

Therefore, you have not fulfilled the information requirement.

In your comments to the draft decision you agree to perform the study and to measure the concentrations of the Substance throughout the whole duration of the test. You indicate that you will prepare water accommodated fractions (WAFs) for each loading rate. You propose to

test a lower concentration series of WAFs to avoid potential interference from the impurities present in the Substance. You propose to prepare WAFs with the technically lowest possible loading rates. You have asked ECHA to confirm your approach.

ECHA takes note of your comment. ECHA does not have a practice of pre-approving study protocols or perform any intermediate evaluations before the deadline in the decision has passed. You should follow the available and recommended guidelines and guidance when preparing the final study design. In particular, you should refer to paragraph 22 of OECD TG 201 to select an appropriate concentration series. The concentration series should preferably cover the range causing 5-75 % inhibition of algal growth rate.

Therefore, you must perform a new growth inhibition study on aquatic plants.

Study design

The substance is difficult to test due to its poor water solubility. OECD TG 201 specifies that for difficult to test substances, the OECD Guidance 23 is to be followed. To get reliable results, the substance properties need to be considered when performing the test, in particular with regard to the test design; including exposure system, test solution preparation, and sampling. OECD GD 23 (Table 1) describes testing difficulties related to a specific property of the substance. You may use the approaches described in OECD GD 23 or other approaches if more appropriate for your substance. The approach selected must be justified and documented.

Due to the substance properties it may be difficult to achieve and maintain the exposure concentrations. Therefore, you have to demonstrate that the concentration of the substance is stable throughout the test (i.e. measured concentrations remains within 80-120% of the nominal concentration). If it is not possible to demonstrate the stability, you must express the effect concentration based on measured values as described in the applicable test guideline. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the test solution preparation method applied was sufficient to maximise the concentration of the Substance in the test solution.

Appendix B: Reasons to request information required under Annex IX of REACH

1. Pre-natal developmental toxicity study in a second species

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX to REACH. Annex IX, Section 8.7.2., column 2 provides that the decision on the need to perform a PNDT study on a second species at a tonnage level of 100 to 1000 tonnes per year should be based on the outcome of the PNDT study on a first species and all other relevant and available data.

You have not provided an OECD TG 414 on a second species.

We have identified the following issue(s):

As already mentioned above, a PNDT study on a second species is needed, if there is a concern for developmental toxicity based on the results from the PNDT study on a first species and other relevant data.

You consider that no developmental toxicity was observed in the available studies: "*There is no evidence of substance-related effects with regard to reproductive toxicity, especially there is no indication for developmental toxicity/teratogenicity based on the available Combined repeated dose toxicity study with the Reproduction/Developmental Toxicity Screening Test (OECD 422), the Prenatal Developmental Toxicity study (OECD 414) as well as the Repeated Dose 90-Day Toxicity study (OECD 408) in rats.*"

However, there is a concern based on information from a first species and taking all the available information into account as required in column 2 at Annex IX, section 8.7.2. Developmental toxicity was observed in one species (rat) in the available OECD TG 414 study ([redacted] 2016), at dose levels which were not markedly toxic to dams. More specifically:

- The incidence of body weight retarded foetuses was statistically significantly increased in the 30 mg/kg bw/day dose group: retarded body weights were observed in 11% of foetuses compared to 3% of control foetuses, and in 52% of litters compared to 25% of control litters.
- Compared to controls, the absolute placental weights were statistically significantly lower in all treated groups, in a dose-dependent manner, reaching -17% at 30 mg/kg bw/day. Also the relative placental weights were lower in all treated groups, reaching statistical significance at 10 and 30 mg/kg bw/day.
- At visceral examination, malformations in the form of enlarged perimeningeal space and impressed cerebral hemisphere were found in two fetuses at 10 mg/kg bw/day and in one fetus at 30 mg/kg bw/day, respectively. In addition, a dilated 3rd brain ventricle was observed in another fetus in the 30 mg/kg bw/day group.

In your comments, you disagree with the need of a PNDT study in a second species. You consider that the findings are isolated, not dose-related and occurred also in the control group. Therefore you consider that they cannot be attributed to treatment with the Substance. Within the comments, you provided summary tables from the OECD TG 414 study as well as historical control data (HCD) ([redacted] 2013).

However, for the following reasons ECHA does not change its conclusions on the above specific observations raising the concern:

- According to the HCD, the incidence of foetuses retarded in weight is 4.4%. This data

confirms that the concurrent control in the OECD TG 414 study (3% of foetuses retarded in weight) is within the HCD, however it does not explain the increased incidence of body weight retarded foetuses (11%) observed in the OECD TG 414 study in the 30 mg/kg bw/day dose group.

- The HCD does not explain the lower placental weights observed in all treated groups, in a dose-dependent manner, in the OECD TG 414 study.
- No brain malformations were reported in the visceral HCD. Therefore, the HCD does not support your view that the malformations observed in the OECD TG 414 study are not treatment-related. Furthermore, malformations were observed in the two highest dose levels, indicating a dose-response.

Hence, ECHA maintains that the above findings indicate a concern for prenatal developmental toxicity. As the condition of Annex IX, section 8.7.2., column 2 is fulfilled, a pre-natal developmental toxicity study in two species is an information requirement for your registration.

You have provided key studies according to OECD TG 422 ([redacted] 2012) and OECD TG 408 ([redacted] 2016) in your dossier. In these studies, key parameters on structural malformations and variations are not investigated as required in a pre-natal developmental toxicity study (OECD TG 414). Therefore, the provided studies do not fulfil the information requirement.

Information on study design

A PNDT study according to the OECD TG 414 study should be performed in the rabbit or rat as the preferred species. The test in the first species was carried out by using a rodent species (rat). Therefore, a PNDT study in a second species must be performed in the rabbit as preferred non-rodent species.

The study shall be performed with oral[2] administration of the Substance.

2. Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.)

The basic test design of an extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is a standard information requirement under Annex IX to REACH, if the available repeated dose toxicity studies indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. Furthermore, Column 2 defines the conditions under which the study design needs to be expanded.

You have provided an OECD TG 422 study and postulate that the information requirement of EOGRTS is not triggered.

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

An EOGRT study is a standard information requirement under Annex IX to REACH, if the available repeated dose toxicity studies reveal other concerns in relation with reproductive toxicity, such as reduced fertility indicated by reduced number of corpora lutea and consequently live-borns, and difficulties in parturition indicated by prolonged pregnancy and/or parturition.

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

You consider that the available repeated dose toxicity studies do not reveal other concerns in relation with reproductive toxicity: "*reproductive performance of the high dose animals suffered due to the considerably reduced food intake and body weight gain depression and must thus be regarded as secondary effect*", and conclude that "*adverse effects were observed neither on fertility parameters in male and female animals nor on development of the offspring. Therefore, according to Column 1, Section 8.7.3, Annex IX of REACH Regulation an extended one-generation study is not proposed also due to animal welfare reasons.*"

Other concerns in relation with reproductive toxicity are observed in the OECD TG 422 study. More specifically, reproductive function was influenced by the treatment with the test item in the high dose group (100 mg/kg bw/day). Only two females became pregnant with low numbers of corpora lutea and live-borns, and the duration of their pregnancy and parturition were prolonged. There were also two females without corpora lutea in ovaries indicating a delay in ovulation. Copulatory indices were reported to be normal. There was no histopathological findings in male sex organs; however, sperm analysis was not performed in this study (but was normal at 30 mg/kg bw/day in the 90-day study). The second mating of 7 male animals at 100 mg/kg bw/day with not treated females revealed reduced ability to mate. Both the copulatory and fertility indices were low.

Also body weights were reduced in the high dose group of the OECD TG 422 study. You consider "*reduced food consumption and consequently depressed body weight gain in the high dose group is a clear sign of marked toxicity*". However, the exact body weight values are not provided in your documentation to allow an independent evaluation by ECHA. You did not initially submit ECHA data, e.g. from feed restriction studies that would support your assumption that the observed reduced food consumption and reduced body weight gain would affect reproductive function and that the observed effects could be considered only secondary. In your comments to the draft decision you provide numerical information on body weights and feed consumption from OECD TG 422 study and argue that, based on the literature data, observed reproductive toxicity is secondary to low feed consumption and body weights.

In females, the feed consumption was 35 and 28% less than in controls during the 1st and 2nd week, respectively, leading to 11% lower body weights during the premating period. According to [redacted] (2005), 25% reduction on food consumption caused 16% reduction in body weight. The feed consumption and body weights can be considered similar enough for the Substance and in the article of [redacted] (2005) to expect similar reproductive toxicity, taking into account e.g. different rat strains.

For the Substance, at the highest dose level of 100 mg/kg bw/day, 10 out of 12 females showed evidence of copulation (sperm positive) but only 2 out of 10 females were pregnant. This indicates that the copulation/mating was successful. This is contradictory to the results of a second mating with non-treated females, which showed low copulatory and fertility indices. However, the exposure duration of males at the time of second mating is considerably longer than at the time of first mating and that can explain the differences in the results.

From the sperm positive females, at the first mating, only 2 became pregnant and had low numbers of corpora lutea, implants, and live pups, and also prolonged gestation and parturition. This is a severe effect at the 100 mg/kg bw/day.

The results for the Substance are different from those caused by similar feed restriction and low body weight only [redacted] 2005). Pregnancy rate was much higher, 19 out of 20 females were pregnant, when feed was restricted by 25% causing 16% lower body weights compared to females fed *ad lib*. Feed was restricted only in females, not in males, which indicates that such a feed restriction and low body weights in females alone does not affect the number of pregnant females. The number of corpora luteae and implants were 17 and

22% lower, respectively, compared to females fed *ad lib* ([redacted] 2005). The Substance caused more severe effects: in addition to very low number of pregnant females, the numbers of corpora luteae and implants were 37 and 49% less compared to the controls, respectively. The other parameters are not comparable due to differences in study design between OECD TG 422 and [redacted] (2005). Therefore, the numbers of pregnant females, corpora lutea and implants were much more severely affected than after feed restriction only and it is likely that the Substance has contributed to the reduced fertility. The number of pregnant females is accurate but the mean number of corpora lutea and implants are from 2 females only, having considerable amount of uncertainty.

In males, the feed consumption (39-35% vs 34%) and body weight data (15% vs 16%) are comparable at 100 mg/kg bw/day after 2 weeks of exposure (your Substance) or 2 weeks feed restriction ([redacted] 2008). There were no histopathological changes in the testis at the end of the study for your Substance whereas [redacted] (2008) reported a low number of histopathological changes in testes. As there was no mating in [redacted] (2005) study, mating information cannot be compared with information from the Substance. It is noteworthy, however, that at the second mating after a long exposure duration with non-exposed females, the Substance reduced copulation and fertility (no numerical data provided).

Based on the available information it is not possible to conclude on the possible contribution of male fertility in relation to the reduced number of pregnant females (e.g. due to low sperm quality).

Another publication reported that a long feed restriction leading to 30% lower body weights does not cause adverse reproductive changes in SD rats ([redacted] 1993). More specifically, there was no effects on female fertility or the total number of implants per dam. The oestrous cycle was transiently prolonged and number of corpora lutea 20% lower in females with 30% lower body weights. In males, number of sperm was unchanged but the percentage motile sperm was slightly low at all levels of feed restriction (leading to 10, 20 or 30% lower body weight).

In conclusion, reproductive toxicity was observed at 100 mg/kg bw/day leading to low number of pregnant females. The data from the Substance and the literature ([redacted] 2005, [redacted] 2008 and [redacted] 1993) does not support your hypothesis that the observed severe reproductive toxicity (low number of pregnant females) could be secondary to lower feed consumption and low body weight observed after 2 weeks of exposure in OECD TG 422.

Accordingly, the available OECD TG 422 study indicates a concern related to reproductive toxicity within the meaning of Column 1 of Annex IX, Section 8.7.3., and an EOGRT study according to OECD TG 443 as specified in this decision is an information requirement for your registration.

Premating exposure duration and dose-level setting

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

Ten weeks premating exposure duration is required if there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA Guidance. In this specific case ten weeks exposure duration is supported by the lipophilicity of the Substance (logKow = 6.68 at 25°C) to ensure that the steady state in parental animals has been reached before mating.

Therefore, the requested premating exposure duration is ten weeks and you agree in your comments to the draft decision with it.

In order to be compliant and not to be rejected due to too low dose levels, the highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects.

In your initial comments to the draft decision you had considered that the choice of dose setting in a reproductive toxicity study is crucial and therefore had asked ECHA to confirm the proposed dose for the OECD TG 443 study and that it will be suitable to cover the identified information gap. In your comments to proposals for amendment you later acknowledged the steep dose-response curve observed in the OECD TG 422 study, and indicated your willingness to perform another dose-range finding study (OECD TG 421) to facilitate adequate dose-level setting for a compliant main study. Furthermore, you expressed your concern on too narrow spacing factors between dose levels which may lead to difficulties in deriving a NOAEL.

In response, ECHA notes that the detailed experimental design is the responsibility of the Registrant. ECHA does not have a practice of approving experimental protocols nor of intermediate evaluations before the deadline set in this decision has passed. ECHA nevertheless observes the following.

Since the available range-finding study (the OECD TG 422) causes reproductive effects at top dose (without excessive toxicity in the adults, i.e. there was not substantial severity), and not at middle dose, the top dose of the EOGRT study should use the dose from the range-finding study that causes reproductive toxicity.

A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs. The dose response in the available OECD TG 422 study for reproductive toxicity is steep, as there is reproductive toxicity at 100 mg/kg/day, but none at 30 mg/kg/day. Therefore, ECHA recommends that the dose-spacing interval be two- to three-fold to obtain the most informative characterisation of the dose-response relationship.

It is recommended that range-finding results are reported with the main study.

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

In your comments to proposals for amendment you also proposed that if severe effects on fertility were observed in the P0 generation of the EOGRT study, this would be sufficient for classification and labelling and the study could be terminated at P0 generation. But ECHA notes that an OECD TG 443 study does not only investigate fertility but also developmental endpoints, providing information which is necessary for a robust risk assessment, i.e. the NOAEL(s). For this Substance, there is a particular concern for developmental neurotoxicity, with Cohorts 2A and 2B included in the request. Therefore, even if effects on fertility are observed, the study, as requested in this decision, must be completed for a full evaluation of reproductive and developmental endpoints as indicated in OECD TG 443, and for providing the NOAEL in F1 and F2 generations.

Cohorts 1A and 1B

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

Extension of Cohort 1B

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

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

- if there are indications that the internal dose for the registered substance will reach a steady state in the test animals only after an extended exposure (column 2, first paragraph, lit. (b), second indent of Section 8.7.3., Annex IX), or

The use of the substance is leading to significant exposure of consumers (use of PC32) and professionals (e.g. PROCs 4, 5, 8a, 8b, 9, 14, 15, 19). The substance has several uses as process regulator in vulcanisation or polymerisation processes which potentially affect many consumers and professionals.

In addition, there are indications that the internal dose for the Substance will reach a steady state in the test animals only after an extended exposure. Specifically, the logKow for the Substance/metabolite(s) is above 4.5 indicating potential accumulation.

In your comments to the draft decision you do not agree that there is significant exposure to consumers and professionals based on the uses. You state that the substance is used as a flame retardant in articles made of polymer matrix and direct contact to the material does not occur for professional workers or consumers. However, the current IUCLID dossier and the CSR (submission [redacted] of 28 August 2019) do not support your claim. You report many professional and consumer uses of the Substance in a mixture in your dossier.

Therefore, based on the information available at the time of issuing the draft decision, Cohort 1B must be extended.

The F2 generation shall be followed to weaning allowing assessment of nursing and lactation of the F1 parents and postnatal development of F2 offspring. Investigations for F2 pups must be similar to those requested for F1 pups in OECD TG 443 and described in OECD GD 151[3]. It is recommended to aim to 20 litter per dose group in order to have similar statistical power for investigations than in P0 generation.

Cohorts 2A and 2B

Annex IX, Section 8.7.3., column 2 of REACH defines when the study design needs to be expanded. Cohorts 2A and 2B (developmental neurotoxicity) may be required by the Agency in case of particular concerns on (developmental) neurotoxicity justified by e.g. existing information on the substance itself derived from relevant available *in vivo* or non-animal approaches (e.g. abnormalities of the central nervous system, evidence of adverse effects on the nervous system in studies on adult animals or animals exposed prenatally). ECHA Guidance[4] further specifies particular concerns justifying inclusion of Cohorts 2A and 2B. In relation to abnormalities observed in the central nervous system, such concerns include e.g. changes in brain volume or specific neural areas.

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[3] http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2013)10&doclanguage=en

[4] ECHA Guidance R.7a, Appendix R.7.6.-2 EOGRTS Study Design

The criteria to include Cohorts 2A and 2B are met, because existing information on the Substance itself derived from relevant available *in vivo* study (OECD TG 414, [redacted] 2016) shows evidence of developmental neurotoxicity as discussed below.

The OECD TG 414 study reported malformations in the form of enlarged perimeningeal space and impressed cerebral hemisphere in two foetuses at 10 mg/kg bw/day and in one foetus at 30 mg/kg bw/day, respectively. In addition, a dilated 3rd brain ventricle was observed in another foetus in the 30 mg/kg bw/day group. ECHA considers that malformations in the brain of animals exposed *in utero* are adverse effects on the nervous system, and indicative of specific developmental neurotoxicity.

In your comments, you disagree with the inclusion of Cohorts 2A and 2B, as you consider that no abnormalities of the central nervous system have been reported in the available studies. As explained in the reasons for request B.1., the historical control data provided within your comments does not explain the malformations observed in the two highest dose levels in the OECD TG 414 study.

Therefore, there is a particular concern on (developmental) neurotoxicity, and Cohorts 2A and 2B need to be conducted.

Species and route selection

The study must be performed in rats with oral[5] administration.

Further expansion of the study design

No triggers for the inclusion of Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including Cohort 3 if relevant information becomes available from other studies or during the conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex IX. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance[6].

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 in Annex IX to the REACH Regulation.

You have sought to adapt this information requirement based on Annex IX, Section 9.1., Column 2 by stating that further testing is not needed since no adverse effects were observed up to the water solubility of the Substance in the short-term toxicity studies on fish, aquatic invertebrates and algae.

We have assessed this information and identified the following issue:

Under Annex IX, Section 9.1., Column 2, a long-term toxicity to study on aquatic invertebrates must be performed unless the Chemical Safety Assessment demonstrates that risks towards the aquatic compartment arising from the use of the Substance are controlled (as per Annex I, section 0.1). The justification must be documented in the Chemical Safety Assessment.

[5] ECHA Guidance R.7a, Section R.7.6.2.3.2.
[6] ECHA Guidance R.7a, Section R.7.6.

In particular, you must take into account the following elements:

- all relevant hazard information from your registration dossier,
- the outcome of the risk assessment in relation to the uses of the Substance,
- the outcome of the PBT/vPvB assessment including information on relevant degradation products and constituents present in concentration at or above 0.1% (w/w).

Poorly water soluble substances require longer time to reach steady-state conditions. Therefore, short-term aquatic toxicity tests may not give a true measure of toxicity for this type of substances. The results from these tests cannot be used for the hazard assessment, the risk assessment or the PBT/vPvB assessment.

In your dossier, you have provided a study for short-term toxicity on aquatic invertebrates. In this study, no toxic effects on *Daphnia magna* were observed up to the solubility limit of the Substance. However, the Substance is poorly water soluble (water solubility: 0.08 mg/L at 20°C).

As your Substance is poorly water soluble, short-term aquatic toxicity tests are not appropriate to assess the toxicity of poorly water soluble substances. You must perform a long-term toxicity test on aquatic invertebrates.

In your comments to the draft decision you agree to perform the study.

Study design

The substance is difficult to test due to its poor water solubility. OECD TG 201 specifies that for difficult to test substances, the OECD Guidance 23 is to be followed, as described under request A.1.

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 in Annex IX to the REACH Regulation.

You have sought to adapt this information requirement based on both Annex VIII, Section 9.1.3, Column 2 and on Annex IX, Section 9.1., Column 2 by stating that the Substance is "*practically insoluble in aquatic environment*" and that further testing is not needed since no adverse effects were observed up to the water solubility of the Substance in the short-term toxicity studies on fish, aquatic invertebrates and algae.

We have assessed this information and identified the following issues:

Annex IX, Section 9.1.6.1 contains no adaptation based on low or no solubility in water of the substance.

You have justified the adaptation by stating that the Substance is "*practically insoluble in aquatic environment*" based on Annex VIII, Section 9.1.3, Column 2.

Your adaptation in based on Annex VIII, Section 9.1.3, Column 2 and does not apply to the current information requirement of Annex IX.

As specified in Annex IX, Section 9.1., Column 2, a long-term toxicity to study on fish must be performed unless the Chemical Safety Assessment demonstrates that risks towards the

aquatic compartment arising from the use of the Substance are controlled (as per Annex I, section 0.1). The justification must be documented in the Chemical Safety Assessment.

In your dossier, you have provided a study for short-term toxicity on fish. In this study, no toxic effects were observed up to the solubility limit of the substance. However, the Substance is poorly water soluble (water solubility: 0.08 mg/L at 20°C).

As explained above (see Appendix B, section 2), short-term aquatic toxicity tests are not appropriate to assess the toxicity of poorly water soluble substances.

Therefore, your adaptation does not fulfil the information requirement.

In your comments to the draft decision you indicate your disagreement to perform the study. You mention four different arguments:

1) You propose to perform the long-term toxicity tests with aquatic organisms in a sequential testing order. You agree to perform the long-term toxicity study on *Daphnia* (request B.2) and to revise the PNEC and the chemical safety assessment (CSA) after the results of that study are available. You propose to perform the requested long-term toxicity test on fish only if the revised CSA shows that PEC/PNEC >1. You indicate that this testing strategy is mentioned in ECHA Guidance (Guidance on information requirements and chemical safety assessment, Chapter R7b, version 4.0, June 2017) and that ECHA accepted this testing strategy previously for another decision.
2) You indicate that you do not expect exposure of the aquatic compartment.
3) Based on its physico-chemical properties (water solubility of 0.08 mg/L, log Pow of 6.68), you expect the Substance to be of more concern for terrestrial and sediment organisms.
4) You refer to Article 25 of REACH, and claim that further testing on fish, if not justified by the CSA, would not be compatible with animal welfare.

However, ECHA disagrees with these four arguments for the following reasons:

1) For the derivation of $PNEC_{aqua}$, data on at least three trophic levels (fish, aquatic invertebrates, and aquatic plants) are required. As the Substance is poorly soluble, short-term data are not reliable for the derivation of the PNEC. Therefore, long-term or chronic data for at least three trophic levels are needed for deriving $PNEC_{aqua}$. The integrated testing strategy (ITS) for aquatic toxicity presented in ECHA Guidance (Guidance on information requirements and chemical safety assessment, Chapter R7b, section R.7.8.5.3., version 4.0, June 2017) is not applicable as you did not demonstrate that there is a species sensitivity difference between invertebrates and fish. As explained above, short-term data for poorly soluble substances cannot serve as compelling evidence to predict relative differences (or lack of) in species sensitivity required to apply the aquatic ITS. The other ECHA decision you refer to concerns a well soluble substance, it is therefore not comparable to the present Decision.

2) Based on the information reported in your CSA, exposure of the aquatic compartment to the Substance is possible. The Substance is not handled under strictly controlled conditions throughout its life cycle and releases to the aquatic compartment do occur. In particular, wide dispersive uses are reported. Exposure from wide dispersive uses can hardly be controlled.

3) Information on aquatic, terrestrial or sediment toxicity are distinct information requirements in REACH. Information on toxicity to terrestrial or sediment organisms cannot replace the information requirement for long-term toxicity to aquatic

organisms.

4) Article 25 or animal welfare does not constitute as such a valid justification to omit the standard information requirements of Annexes VII – X or a valid adaptation to these information requirements.

Therefore, you must perform a long-term toxicity test on fish.

Study design

The substance is difficult to test due to its poor water solubility. OECD TG 201 specifies that for difficult to test substances, the OECD Guidance 23 is to be followed, as described under request A.1.

5. Simulation testing on ultimate degradation in surface water (Annex IX, Section 9.2.1.2.)

Simulation testing on ultimate degradation in surface water is a standard information requirement at Annex IX to REACH.

You have sought to adapt this information requirement based on Annex IX, Section 9.2.1.2, Column 2.

You have justified the adaptation by stating that:
- the Substance is "*practically insoluble in water*", and
- direct and indirect environmental exposure to the Substance is "*highly unlikely*".

We have assessed this information and identified the following issues:

Annex IX, Section 9.2.1.2, Column 2 states that simulation testing on ultimate degradation in surface water does not need to be conducted if the substance is highly insoluble in water.

Screening information provided in your dossier indicates that the Substance has a water solubility of 0.08 mg/L (i.e. 80 µg/L) at 20°C.

ECHA does not consider the Substance to be highly insoluble in water for the purpose of testing its ultimate degradation in surface water. The test concentration recommended in OECD TG 309 is less than 1 µg/L to 100 µg/L. The water solubility of the Substance is more than 1 µg/L. Therefore, simulation testing in surface water is technically feasible with the Substance.

Annex XIII, Section 2.1 of REACH indicates that additional information for the identification of PBT/vPvB substances may be omitted if the Substance is handled under strictly controlled conditions and is not released throughout its life cycle. The Substance must then be regarded as if it is a PBT or vPvB substance in the registration dossier.

You have claimed that direct and indirect exposure to the Substance is "*highly unlikely*".

Annex IX, Section 9.2.1.2., Column 2 contains no provision allowing to omit the information requirement based on unlikely exposure. ECHA understands that you may have sought to adapt the information requirement based on Annex XIII, Section 2.1. However, based on the information reported in your chemical safety assessment, the Substance is not handled under strictly controlled conditions throughout its life cycle and environmental releases do occur. In

particular, you have reported wide dispersive uses, which can hardly be controlled. Furthermore, you have not regarded the Substance as if it is PBT or vPvB.

Therefore, your adaptation does not fulfil the information requirement.

In your comments to the draft decision, you explain that the Substance is already assumed to be persistent in your chemical safety assessment. For this reason, you consider that no further testing is needed for assessing the persistence of the Substance.

You further explain that, if you are required to perform the tests, you will perform these tests sequentially taking into account the physico-chemical properties of the Substance, the available data and the relevance of the different compartments. You suggest starting with a test in sediment (request B.6).

Section 2.1. of Annex XIII specifies that "*no additional information needs to be generated for the assessment of PBT/vPvB properties if there is no indication of P or B properties following the result from the screening test or other information*".

Based on the available information, the Substance is not readily biodegradable. Therefore, it is potentially persistent (P) or very persistent (vP). Similarly, with a log Kow value of 6.68, the Substance could potentially be bioaccumulative (B) or very bioaccumulative (vB) (see request B.8 of the draft decision).

Therefore, the available information does not rule out P or B properties; the Substance is potentially PBT/vPvB.

Section 2.1. of Annex XIII also indicates that further testing may be omitted for the purpose of the PBT/vPvB assessment if "*the process and use conditions of the substance meet the conditions as specified in Section 3.2(b) or (c) of Annex XI* [i.e. if the Substance is handled under strictly controlled conditions throughout its life cycle and is not released during its life cycle]*, and subsequently the substance is considered as if it is a PBT or vPvB in the registration dossier*".

Based on the information reported in your chemical safety assessment, environmental exposure to the Substance is possible, for the water, sediment and soil compartments. The Substance is not handled under strictly controlled conditions throughout its life cycle and environmental releases do occur. You have reported wide dispersive uses, which can hardly be controlled. You do not handle the Substance as if it is a PBT or vPvB.

Therefore, further testing cannot be omitted for the purpose of the PBT/vPvB assessment. You should refer to Appendix D of this decision for defining your testing strategy.

Therefore, you must perform simulation testing on ultimate degradation in surface water.

Study design

Under Annex XIII, the information must be based on data obtained under conditions relevant for the PBT/vPvB assessment. Therefore:

- You must perform the OECD TG 309 test, by following the pelagic test option with natural surface water containing approximately 15 mg dw/L of suspended solids (acceptable concentration between 10 and 20 mg dw/L) (ECHA Guidance R.11).

- You must perform the test at the temperature of 12 °C, the average environmental temperature for the EU (ECHA Guidance R.16, Table R.16-8). Performing the test at this temperature is in line with the applicable test conditions of OECD TG 309.

Non-extractable residues (NER) must be quantified in all simulation studies. The reporting of results must include a scientific justification of the used extraction procedures and solvents. By default, total NER is regarded as non-degraded Substance. However, if reasonably justified and analytically demonstrated a certain part of NER may be differentiated and quantified as irreversibly bound or as degraded to biogenic NER. Such fractions could be regarded as removed when calculating the degradation half-life(s) (ECHA Guidance Chapter R.11).

Under Annex XIII, you must assess the PBT/vPvB properties of the relevant constituents of the Substance. Therefore, the persistence of each relevant constituent present in concentrations at or above 0.1% (w/w) or, if not technically feasible, in concentrations as low as technically detectable must be assessed. Alternatively, you would have to justify why you consider these not relevant for the PBT/vPvB assessment.

6. Soil simulation testing (Annex IX, Section 9.2.1.3.)

Soil simulation testing is a standard information requirement at Annex IX of REACH for substances with a high potential for adsorption to soil. The Substance has a high adsorption coefficient (log Koc: 4.2 at 25°C), indicating high adsorptive properties.

You have sought to adapt this information requirement based on Annex IX, Section 9.2.1.3, Column 2.

You have justified the adaptation by stating that:
- the Substance is "*practically insoluble in water*", and
- direct and indirect environmental exposure to the Substance is "*highly unlikely*".

We have assessed this information and identified the following issues:

Annex IX, Section 9.2.1.2., Column 2 contains no provision allowing to omit the information requirement based on low on or no water solubility of the substance.

Contrary to your claim, the low water solubility of the Substance does not prevent soil simulation testing. For example, OECD TG 307 explicitly indicates that it is applicable to water-insoluble compounds.

Annex IX, Section 9.2.1.3, Column 2 states that simulation testing on soil does not need to be conducted if direct or indirect exposure of soil is unlikely.

You have claimed that exposure of soil is low and in particular that "*no sludge application from STP on soil will be done*".

However, based on the information reported in your chemical safety assessment, environmental exposure to the Substance is likely. The Substance is not handled under strictly controlled conditions throughout its life cycle and environmental releases do occur. For example, you have reported wide dispersive uses, which can hardly be controlled. In particular, exposure to STP sludge and then to soil cannot be ruled out for wide dispersive uses. Also for industrial uses, your risk assessment shows that releases to soil are possible. For example, for exposure scenario 7 ("*Use of reactive process regulators in polymerisation processes at industrial site (inclusion or not into/onto article)*") as well as for combined

exposure due to all widespread uses, risk characterisation ratios [redacted] are reported for agricultural soil, indicating that exposure of soil is likely and significant.

Therefore, your adaptation does not fulfil the information requirement.

In your comments to the draft decision, you explain that the Substance is already assumed to be persistent in your chemical safety assessment. For this reason, you consider that no further testing is needed for assessing the persistence of the Substance.

You further explain that, if you are required to perform the tests, you will perform these tests sequentially taking into account the physico-chemical properties of the Substance, the available data and the relevance of the different compartments. You suggest starting with a test in sediment (request B.6).

As explained in request B.4 above, ECHA considers that the requested test cannot be omitted for the purpose of the PBT/vPvB assessment. You should refer to Appendix D of this decision for defining your testing strategy.

Therefore, you must perform soil simulation testing.

Study design

OECD TG 307 is an appropriate method for studying the degradation in soil. The requested simulation test must be performed under relevant conditions (12°C) and non-extractable residues (NER) must be quantified, for the reasons explained above in Appendix B, section 4. The biodegradation of each relevant constituent present in concentration at or above 0.1% (w/w) or, if not technically feasible, in concentrations as low as technically detectable, must be assessed. This can be done simultaneously during the same study. Alternatively, you would have to justify why you consider these not relevant for the PBT/vPvB assessment.

7. Sediment simulation testing (Annex IX, Section 9.2.1.4.)

Sediment simulation testing is a standard information requirement at Annex IX of REACH for substances with a high potential for adsorption to soil. The Substance has a high adsorption coefficient (log Koc: 4.2 at 25°C), indicating high adsorptive properties.

You have sought to adapt this information requirement based on Annex IX, Section 9.2.1.4, Column 2.

You have justified the adaptation by stating that:
- the Substance is "*practically insoluble in water*", and
- direct and indirect environmental exposure to the Substance is "*highly unlikely*".

We have assessed this information and identified the following issues:

Annex IX, Section 9.2.1.4., Column 2 contains no provision allowing to omit the information requirement based on low on or no water solubility of the Substance.

Contrary to your claim, the low water solubility of the Substance does not prevent sediment simulation testing. For example, OECD TG 308 explicitly indicates that it is applicable to poorly water-soluble compounds.

Annex IX, Section 9.2.1.4, column 2 states that simulation testing on sediment does not need to be conducted if direct or indirect exposure of sediment is unlikely.

You have claimed that exposure of sediment is "*highly unlikely*".

However, based on the information reported in your chemical safety assessment, environmental exposure to the Substance is likely. The Substance is not handled under strictly controlled conditions throughout its life cycle and environmental releases do occur. For example, you have reported wide dispersive uses, which can hardly be controlled. Also for industrial uses, your risk assessment shows that releases to sediment are possible. For example, for exposure scenarios 3 ("*Formulation or re-packing - Distribution of substance*") and 6 ("*Use at industrial sites - Synthesis; Industrial use*"), risk characterisation ratios [redacted] are reported for freshwater sediment, indicating that exposure of sediment is likely and significant.

Therefore, your adaptation does not fulfil the information requirement.

In your comments to the draft decision, you explain that the Substance is already assumed to be persistent in your chemical safety assessment. For this reason, you consider that no further testing is needed for assessing the persistence of the Substance.

You further explain that, if you are required to perform the tests, you will perform these tests sequentially taking into account the physico-chemical properties of the Substance, the available data and the relevance of the different compartments. You suggest starting with the test in sediment.

As explained in request B.4 above, ECHA considers that the requested test cannot be omitted for the purpose of the PBT/vPvB assessment. You should refer to Appendix D of this decision for defining your testing strategy.

Therefore, you must perform sediment simulation testing.

Study design

OECD TG 308 is an appropriate method for studying the degradation in sediment. The requested simulation test must be performed under relevant conditions (12°C) and non-extractable residues (NER) must be quantified, for the reasons explained above in Appendix B, section 4. The biodegradation of each relevant constituent present in concentration at or above 0.1% (w/w) or, if not technically feasible, in concentrations as low as technically detectable, must be assessed. This can be done simultaneously during the same study. Alternatively, you would have to justify why you consider these not relevant for the PBT/vPvB assessment.

8. Identification of degradation products (Annex IX, 9.2.3.)

Identification of the degradation products is a standard information requirement at Annex IX of REACH unless the substance is readily biodegradable.

You have not provided any information on the identification of degradation products, nor an adaptation in accordance with column 2 of Annex IX, Sections 9.2 or 9.2.3. or with the general rules of Annex XI for this standard information requirement. Screening information (OECD TG 301D) provided in your dossier indicates only 0.2 % biodegradation in 28 days.

The Substance is not readily biodegradable and you have not provided any justification in your chemical safety assessment or in the dossier for why there is no need to provide information on the degradation products.

Therefore, your dossier does not fulfil the information requirement.

In your comments to the draft decision, you explain that the Substance is already assumed to be persistent in your chemical safety assessment. For this reason, you consider that no further information is needed for assessing the persistence of the Substance. You also claim that the identification of degradation products would not be technically feasible.

As explained in request B.4 above, ECHA considers that the requested information cannot be omitted for the purpose of the PBT/vPvB assessment. Furthermore, you have not justified why you consider the identification of degradation products not technically feasible.

Therefore, you must provide information on the identification of degradation products.

Study design

Regarding appropriate and suitable test method, the methods will have to be substance-specific. Identity, stability, behaviour, and molar quantity of the degradation/transformation products relative to the Substance must be evaluated and reported, when analytically possible. In addition, degradation half-life, log Kow and potential toxicity of the transformation/degradation may be investigated. You may obtain this information from the 3 degradation studies also requested in this Decision (see Appendix B, sections 4 - 6) or any other appropriate method. You must provide a scientifically valid justification for the chosen method.

9. Bioaccumulation in aquatic species (Annex IX, Section 9.3.2.))

Bioaccumulation in aquatic species, preferably fish is a standard information requirement at Annex IX of REACH.

You have sought to adapt this information requirement based on Annex IX, Section 9.3.2., Column 2.

You have justified the adaptation by stating that:
- direct and indirect environmental exposure to the Substance is "*highly unlikely*", and
- the Substance is "*practically insoluble in water*".

In addition, you have provided predictions obtained from two QSAR models.

We have assessed this information and identified the following issues:

A. Annex IX, Section 9.3.2., Column 2, provides that bioaccumulation testing does not need to be conducted if direct and indirect exposure of the aquatic compartment is unlikely.

You have claimed that direct and indirect exposure to the Substance is "*highly unlikely*".

Based on the information reported in your chemical safety assessment, environmental exposure to the Substance is likely. The Substance is not handled under strictly controlled conditions throughout its life cycle and environmental releases do occur. In particular, you have reported wide dispersive uses, which can hardly be controlled.

B. Annex XI, Section 2 indicates that this standard information requirement may be omitted if it is not technically possible to conduct the study as a consequence of the

properties of the Substance.

You claim that the Substance is "*practically insoluble in water*".

Annex IX, Section 9.3.2., Column 2 contains no provision allowing to omit the bioaccumulation testing based on low or no solubility in water.

In addition, we understand that you may have argued that the insolubility of the Substance means that it is technically not possible to conduct a bioacccumulation test. However, the low water solubility of the Substance does not prevent a bioaccumulation study to be conducted. The Substance has a water solubility of 0.08 mg/L at 20°C. The first part of OECD TG 305 (305-I) describes an aqueous exposure bioconcentration test which is generally recommended for substances with a water solubility above ~0.01 – 0.1 mg/L. OECD TG 305 also incorporates a dietary bioaccumulation test (305-III) which is suitable for substances with a water solubility below that range of ~0.01 – 0.1 mg/L. The water solubility of the Substance being in that range, both methods may be feasible (see below paragraph on which test method to use).

C. Under Section 2. of Annex XIII, results obtained from QSAR models can be used as screening information, but not as assessment information.

Annex XIII of REACH makes the distinction between 'screening information' and 'assessment information'.

Section 2.1. of this Annex specifies that "*no additional information needs to be generated for the assessment of PBT/vPvB properties if there is no indication of P or B properties following the result from the screening test or other information*". Therefore, as long as a piece of screening information indicates that the substance could potentially be persistent (P) and bioaccumulative (B), then further information, i.e. 'assessment information', needs to be generated.

A log Kow higher than 4.5 constitutes screening information which indicates that a substance could potentially be bioaccumulative or very bioaccumulative (Section 3.1.2. of Annex XIII of REACH and Chapter R.11 of the ECHA Guidance on information requirements and chemical safety assessment (version 3.0, June 2017))

Results from a bioconcentration or bioaccumulation study in aquatic species can constitute assessment information for B or vB properties (Section 3.2.2. of Annex XIII of REACH).

You have provided BCF predictions obtained from two QSAR models:
- BCF value of 999 using model CAESAR v2.1.14 in program VEGA v1.1.4.
- BCF value of 1275 using model T.E.S.T. v4.2.1.

An experimental log Kow value of 6.68 is reported for the Substance.

For the PBT/vPvB assessment presented in section 8 of your chemical safety report, you have used the value of 1275 predicted by model T.E.S.T. v4.2.1 as a key value for the bioaccumulation of the Substance. Based on this value, you have considered that the Substance was not bioaccumulative (B). You concluded that the Substance was neither PBT nor vPvB.

ECHA disagrees with your conclusion for the following reasons:

- The experimental log Kow value of 6.68 is a valid piece of screening information that shows that the Substance could potentially be bioaccumulative or very

bioaccumulative.

- QSAR results do not constitute assessment information for the B/vB assessment. Therefore, BCF predictions obtained from QSAR models do not supersede the screening information represented by the log Kow of 6.68 for the B/vB assessment. It is not possible to conclude that the Substance is not B/vB.

- The two QSAR results you have provided are highly uncertain. The confidence intervals for the predicted values are very large for both results. The higher bounds of the confidence intervals are largely exceeding 2000 and sometimes even 5000 for most of the predictions calculated by the models included in T.E.S.T. as well as for the value predicted by CAESAR. Furthermore, some alternative models, not mentioned in your dossier, predict BCF values above 2000 if not 5000 (e.g. Dimitrov model in CATALOGIC or BCFWIN model in EPISuite). Therefore, the QSAR results you have provided are inconclusive for the B/vB assessment, even as screening information.

Therefore, the Substance is potentially B/vB.

Similarly, the Substance is potentially persistent (P) or very persistent (vP) (see Appendix B, sections 4-7 above). High toxicity (T criterion) (see Appendix A, section 1 and Appendix B, sections 2-3 above) cannot be ruled out either.

Therefore, the Substance is potentially PBT/vPvB.

Therefore, your adaptation does not fulfil the information requirement and further information on bioaccumulation is required.

In your comments to the draft decision you agree to perform the study.

Study design

Bioaccumulation in fish: aqueous and dietary exposure (test method EU C.13. / OECD TG 305) is the preferred test to investigate bioaccumulation (ECHA *Guidance, Chapter R.7c, R.7.10.3.1*).

Whenever technically feasible, the aqueous route of exposure (OECD TG 305-I) must be used as the results obtained can be used directly for comparison with the B and vB criteria of Annex XIII of REACH. If testing through aquatic exposure is technically not possible, you must provide scientifically valid justification for the infeasibility.

OECD TG 305 recommends that an aqueous exposure test (OECD TG 305-I) should be considered as long as the water solubility remains significant with respect to the sensitivity of the available analytical techniques. In practice, the choice of which test method to use would rely on whether it is possible to prepare stable, measurable dissolved aqueous concentrations applicable for an aqueous exposure study.

In case you conduct the study using the dietary exposure route (OECD 305-III), you must also attempt to estimate the corresponding BCF value from the dietary test data according to Annex 8 of the OECD 305 TG and OECD Guidance Document on Aspects of OECD TG 305 on Fish Bioaccumulation, ENV/JM/MONO (2017)16. In any case you must report all data derived from the dietary test as listed in the OECD TG 305-III.

Appendix C: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

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

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

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[7].

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. Selection of the Test material(s)
   The Test Material used to generate the new data must be selected taking into account the following:
   - the variation in compositions reported by all members of the joint submission,
   - the boundary composition(s) of the Substance,
   - the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

2. Information on the Test Material needed in the updated dossier
   - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[8].

[7] https://echa.europa.eu/practical-guides
[8] https://echa.europa.eu/manuals

Appendix D: General recommendations when conducting and reporting new tests for REACH purposes

A. Strategy for the PBT/vPvB assessment

You are advised to consult ECHA Guidance R.7b (Section R.7.9.), R.7c (Section R.7.10) and R.11 on PBT assessment to determine the sequence of the tests needed to reach the conclusion on PBT/vPvB. The guidance provides advice on 1) integrated testing strategies (ITS) for the P, B and T assessments and 2) the interpretation of results in concluding whether the Substance fulfils the PBT/vPvB criteria of Annex XIII.

In particular, you are advised to first conclude whether the Substance fulfils the Annex XIII criteria for P and vP, and then continue with the assessment for bioaccumulation. When determining the sequence of simulation degradation testing you are advised to consider the intrinsic properties of the Substance, its identified uses and release patterns as these could significantly influence the environmental fate of the Substance. You must revise your PBT assessment when the new information is available.

Appendix E: Procedure

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

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

The compliance check was initiated on 17 April 2019.

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

ECHA took into account your comments and did not amend the request(s) but amended the deadline.

Deadline change

The timeline indicated in the initial draft decision was to provide the information requested under B.2. (extended one-generation reproductive toxicity study, OECD TG 443) by 24 months from the date of adoption of the decision, and all other information by 42 months from the date of adoption of the decision.

In your comments on the initial draft decision, you requested an extension of the timeline to 50 months for "*higher tier (eco)-toxicological studies (e.g. OECD 443, OECD 210).*" You justified your request stating that contract research organisation (CRO) capacity related to the requested information is limited, and provided supporting documentation by a CRO confirming 50 months is sufficient for conducting the testing requested in the decision (excluding the preparations related to radiolabeling of the test material). You provided another supporting documentation from a CRO specifying the time constraints related to radiolabeling will require 4 months from placing an order.

ECHA notes the provided documentation does not specify the timeline required for conducting an extended one-generation reproductive toxicity study (B.2), and that conducting the study does not require radiolabeling of the test material.

Because of the incomplete supporting documentation and different timelines initially set for information requested in the decision, the timeline for the information requested under B.2. was not amended while the timeline for all other information requested in this decision is extended to 50 months.

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. The timeline for providing the requested information was modified accordingly.

Following a proposal for amendment, a request for a pre-natal developmental toxicity study in a second species was included in the decision (request B.1.). In accordance with ECHA's practice, the timeline to provide information requested under B.1. and B.2. was modified to 30 months.

ECHA invited you to comment on the proposed amendment(s) and referred the modified draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee. In your comments, you requested an extension of the timeline from 30 to 36 months for providing the OECD TG 443 study, including a new dose-range finding study (OECD TG 421 or similar). You justified your request with limited laboratory capacity. Upon request, you provided supporting documentation from a CRO confirming that 36 months is sufficient for conducting these tests. The timeline for the information requested under B.1. and B.2. was modified to 36 months.

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-73 meeting and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix F: List of references - ECHA Guidance[9] and other supporting documents

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

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

Read-across assessment framework (RAAF, March 2017)[10]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[10]

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

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

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

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

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

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

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

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

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[11]

[9] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[10] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[11] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

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

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

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.