EUROPEAN CHEMICALS AGENCY

Helsinki, 25 October 2017

Addressee: [redacted]

Decision number: CCH-D-2114375721-47-01/F
Substance name: 1,3-diethyldiphenylurea
EC number: 201-645-2
CAS number: 85-98-3
Registration number: [redacted]
Submission number: [redacted]
Submission date: 31/08/2016
Registered tonnage band: 100-1000

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

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

2. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

3. **Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.; test method: EU B.56./OECD TG 443) in 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; and**
   - **Cohorts 2A and 2B (Developmental neurotoxicity).**

4. **Simulation testing on ultimate degradation in surface water (Annex IX, Section 9.2.1.2.; test method: Aerobic mineralisation in surface water – simulation biodegradation test, EU C.25./OECD TG 309) at a temperature of 12 °C with the registered substance;**

5. **Bioaccumulation in aquatic species (Annex IX, Section 9.3.2.; test method: Bioaccumulation in fish: aqueous and dietary exposure, OECD TG 305, aqueous exposure) with the registered substance.**

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

You have to submit the requested information in an updated registration dossier by **4 May 2020**. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

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

Appeal

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

Authorised[1] by 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

TOXICOLOGICAL INFORMATION

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

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

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

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

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

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

You have provided as the key study a reference to a publication entitled "*Salmonella mutagenicity tests, IV. Results from testing of 300 chemicals*" from the year 1988 with an assigned reliability score of 2. You indicate test guideline according to Mortelmans, K., Zeiger, E., Ames Salmonella/microsome mutagenicity assay, Mutat Res. 2000 Nov 20, 455 (1-2), 29-60. The test used four different strains of *S. typhimurium* TA 1535, TA 97, TA 98 and TA 100 and it did not include tests with strains S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). However, since the test was conducted, significant changes have been made to OECD TG guideline 471 so that additionally testing with S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) is now required. Therefore, the provided study does not meet the current guidelines, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation.

According to paragraph 13 of the current OECD TG 471 test guideline (updated 1997) at least five strains of bacteria should be used: S. typhimurium TA1535; TA1537 or TA97a or TA97; TA98; TA100; S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). This includes four strains of *S. typhimurium* (TA1535; TA1537 or TA97a or TA97; TA98; and TA100) that have been shown to be reliable and reproducibly responsive between laboratories.

These four *S. typhimurium* strains have GC base pairs at the primary reversion site and it is known that they may not detect certain oxidising mutagens, cross-linking agents and hydrazines. Such substances may be detected by E.coli WP2 strains or *S. typhimurium* TA102 which have an AT base pair at the primary reversion site.

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

In addition, the study does not provide the information required by Annex VIII, Section 8.4.1., because the reported top dose (1 mg/plate) is lower than recommended and without further justification or considerations in accordance with the OECD TG 471. According to OECD TG 471, "*the recommended maximum test concentration for soluble non-cytotoxic substances is 5 mg/plate or 5 ml/plate. For non-cytotoxic substances that are not soluble at 5 mg/plate or 5 ml/plate, one or more concentrations tested should be insoluble in the final treatment mixture. Test substances that are cytotoxic already below 5 mg/plate or 5 ml/plate should be tested up to a cytotoxic concentration. The precipitate should not interfere with the scoring.*" In particular, the following elements are missing in IUCLID reporting which would be required in order to confirm e.g. appropriate dosing used in the study and the results: experimental data indicating mutant frequencies and cytotoxicity (preferably in tabulated form). Therefore, contrary to Article 3(28) of the REACH Regulation, the adequate and reliable documentation of the study is not provided and therefore an independent assessment of the adequacy of this study, its results and its use for hazard assessment is not possible.

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

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

In your comments following the procedure set out in Article 50(1) of the REACH Regulation you have indicated your agreement to conduct the test requested in the draft decision.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471).

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

A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement. You provided the following justification for the adaptation: "*Prenatal Developmental Toxicity Study does not need to be conducted as short-term toxicity study (28 days) and reliable sub-chronic toxicity study (90 days) are available that indicate no adverse effects on reproductive organs and tissues and Reproduction/Developmental Toxicity Screening Test indicates no adverse effects on parental males (rats), females and offspring.*"

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.2. – Weight of evidence.

However, ECHA notes that your adaptation does not meet the general rules for adaptation of Annex XI; Section 1.2. because the studies you have provided, i.e. a repeated dose toxicity study (28-day) (test method: EU B.7), a repeated dose toxicity study (90-day) (test method: EU B.26) and a reproduction/developmental toxicity screening test (test method: OECD TG 421), do not cover key parameters of a pre-natal developmental toxicity study, such as examination of foetuses for skeletal and visceral alteration. Therefore, your adaptation of the information requirement is rejected.

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

According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

In your comments following the procedure set out in Article 50(1) of the REACH Regulation you have indicated your agreement to conduct the test requested in the draft decision.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a first species (rat or rabbit) by the oral route.

3. Extended one-generation reproductive toxicity study (Annex IX, 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 IX of the REACH Regulation, if the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD TGs 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. If the conditions described in column 2 of Annex IX 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 in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

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

You did not consider the information requirement for reproductive toxicity in Annex IX, Section 8.7.3., column 1, because no adverse effects on reproductive organs or tissues have been observed in the available repeated dose toxicity studies: "*In accordance with column 1 of REACH Annex IX, section 8.7.3 the two-generation reproductive toxicity study (one species, male and female, most appropriate route of administration, having regard to the likely route of exposure) does not need to be conducted as a reliable short-term toxicity study (28 days) and sub-chronic toxicity study (90 days) are available that indicate no adverse effects on reproductive organs and tissues.*"

However, ECHA points out that the information requirement according to Annex IX, Section 8.7.3. has been changed by Commission Regulation (EU) 2015/282, and that the new information requirement, i.e. the extended one-generation reproductive toxicity study, is an information requirement if adverse effects on reproductive organs or tissues have been observed in the available repeated dose toxicity studies (e.g. a 28-day or 90-day repeated dose toxicity study, OECD 421 or 422 screening studies) or if these studies reveal other concerns in relation with reproductive toxicity. ECHA considers that such concerns in relation with reproductive toxicity are observed from the above studies. More specifically, in the provided reproductive toxicity screening study (OECD TG 421) with the registered substance ([redacted], 2012), you have reported that "*the proportion of morphologically changed sperms was slightly increased in treated males in dose-dependent manner. The detailed histological examination of spermatogenesis stages did not even ascertain any damage. But the animals in the reproduction screening study are treated for less than the duration of the spermatogenic cycle so that an effect on spermatogenesis may not have had adequate time to become evident as reduced sperm counts that affect fertility*".

Hence, ECHA considers that on the basis of your considerations set out above such a concern needs to be be investigated in a definitive study for reproductive toxicity that has more statistical power and longer exposure duration than the screening study (OECD TG 421/422).

Therefore, an extended one-generation reproductive toxicity study is an information requirement.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently, there is an information gap and it is necessary to provide information for this endpoint. Thus, an extended one-generation reproductive toxicity study according to Annex IX, Section 8.7.3., is required. The following refers to the specifications of this required study.

b) The specifications for the required study

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 the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017), the starting point for deciding on the length of the 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 on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017). As explained below under section 4, ECHA considers that log KoW value for the registered substance could potentially be above 4.5. Hence, ten weeks exposure duration is supported also by the lipophilicity of the substance to ensure that the steady state in parental animals has been reached before mating.

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 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 IX. 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 available *in vivo* 90-day study ([redacted], 2016) show evidence of specific mechanisms/modes of action of the substance with an association to (developmental) neurotoxicity. More specifically, the value of cholinesterase increased significantly in a dose-dependent manner in all male treated groups and the value was above historical control limits at the mid (150 mg/kg bw/day) and high dose level (600 mg/kg/day). In addition, a similar effect was reported in male treated satellite group.

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.

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 on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

c) Outcome

Based on the available information, 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 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; and
- Cohorts 2A and 2B (Developmental neurotoxicity);

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B and/or Cohort 3 if relevant 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 IX and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 6.0, July 2017). 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.

In your comments following the procedure set out in Article 50(1) of the REACH Regulation you have indicated your agreement to conduct the test requested in the draft decision.

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

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

"Simulation testing on ultimate degradation in water" is a standard information requirement as laid down in Annex IX, section 9.2.1.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

In the technical dossier, you have provided a study record for a non-guideline study that investigated the microbial degradation and biotransformation of the registered substance and of a number of other compounds present in wastewaters from the manufacture of ball-grain powder. This study was conducted under both aerobic and anaerobic conditions and in both static (batch) and continuous culture systems. For the aerobic study, anaerobic sewage sludge with an equal volume of activated sludge was used as inoculum. For the anaerobic study, anaerobic sewage sludge with an equal volume of water was used.

The concentration of the registered substance was observed to be reduced to approximately [redacted]% of its initial concentration after 5 days, under aerobic conditions in static culture and in the presence of a rich nutrient medium. N-ethylaniline and ethylphenylurea were identified as transformation products. Increasing the concentrations of nutrients or carbon source supplements increased the disappearance of the substance. Under anaerobic conditions, the substance appeared to be quite stable.

You have also provided (Q)SAR predictions from the following two models:

- BIOWIN 2 (Non-linear model prediction) predicts fast degradation of the registered substance
- BIOWIN 3 (Ultimate biodegradation timeframe prediction) predicts degradation of the registered substance within weeks/months.

For your assessment, you have concluded that the substance is not persistent though you have acknowledged it is not readily biodegradable.

ECHA notes that the experimental study you provided is not a guideline study. It was conducted under conditions that are not representative of environmental conditions (e.g., the inoculum was prepared from sewage sludge and activated sludge and a rich nutrient medium was used). Furthermore, the ultimate degradation of the registered substance was not investigated: only disappearance of the substance was measured but not its mineralisation. Therefore, this study cannot be considered equivalent to a simulation testing on ultimate degradation in surface water and does not rule out the possibility that the substance could be persistent in surface water.

ECHA further notes that the two (Q)SAR results you have provided, do not allow either to conclude that the substance is not persistent. ECHA Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.11 on PBT/vPvB assessment, proposes criteria to interpret (Q)SAR results for the purpose of the persistence assessment (see Table R.11—4: Screening information for P and vP). In particular, ECHA notes that you have not considered the results of the BIOWIN 6 (MITI non-linear model) model. BIOWIN 6 predicts that the registered substance will not biodegrade fast (predicted probability of rapid biodegradation is 0.0422). ECHA also notes that BIOWIN 3 (Ultimate survey model) predicts an ultimate biodegradation timeframe value of 2.6501 (weeks/months). According to Table R.11—4 of the ECHA Guidance no conclusion with regard to the persistence assessment is possible from these QSAR results and further information is necessary.

Therefore, ECHA concludes that the information provided does not provide the information required by Annex IX, Section 9.2.1.2.

ECHA notes that Column 2 of Section 9.2. of Annex IX of the REACH Regulation specifies that simulation tests need to be conducted if the chemical safety assessment (CSA) according to Annex I of the REACH Regulation 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 on the results of the CSA.

As explained above, ECHA considers that no adequate information is available with regard to the potential persistence of the substance.

ECHA further notes that no adequate information is available with regard to the potential bioaccumulation of the substance (see section 5 of the present decision). It is therefore not possible to conclude whether the substance meets or not the B/vB criterion for the PBT/vPvB assessment as detailed in Annex XIII of the REACH Regulation.

ECHA finally notes that information is missing on reproductive toxicity for the registered substance (see issues 2 and 3 of the present decision). Therefore, it is not possible to conclude whether the substance meets or not the T criteria for the PBT assessment as detailed in Annex XIII of the REACH Regulation.

Therefore, ECHA considers that your CSA does not rule out the possibility that your substance could be PBT or vPvB and that you need to investigate further the degradation of your substance.

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.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b*, Aerobic mineralisation in surface water – simulation biodegradation (test method EU C.25. / OECD TG 309) is the preferred test to cover the standard information requirement of Annex IX, Section 9.2.1.2.

One of the purposes of the simulation test is to provide the information that must be considered for assessing the P/vP properties of the registered substance in accordance with Annex XIII of the REACH Regulation to decide whether it is persistent in the environment. Annex XIII also indicates that "*the information used for the purposes of assessment of the PBT/vPvB properties shall be based on data obtained under relevant conditions*". The Guidance on information requirements and chemical safety assessment R.7b specifies that simulation tests "*attempt to simulate degradation in a specific environment by use of indigenous biomass, media, relevant solids* [...]*, and a typical temperature that represents the particular environment*". The Guidance on information requirements and chemical safety assessment Chapter R.16 on Environmental Exposure Estimation, Table R.16-8 (version 3.0 February 2016) indicates 12°C (285K) as the average environmental temperature for the EU to be used in the chemical safety assessment. Performing the test at the temperature of 12°C is within the applicable test conditions of the Test Guideline OECD TG 309. Therefore, the test should be performed at the temperature of 12°C.

In the OECD TG 309 Guideline, two test options, the "pelagic test" and the "suspended sediment test", are described. ECHA considers that the pelagic test option should be followed as that is the recommended option for P assessment. The amount of suspended solids in the pelagic test should be representative of the level of suspended solids in EU surface water. The concentration of suspended solids in the surface water sample used should therefore be approximately 15 mg dw/L.

Testing natural surface water containing between 10 and 20 mg SPM dw/L is considered acceptable. Furthermore, when reporting the non-extractable residues (NER) in your test results you should explain and scientifically justify the extraction procedure and solvent used obtaining a quantitative measure of NER.

In your comments following the procedure set out in Article 50(1) of the REACH Regulation, you proposed to wait for the outcome of the revised bioaccumulation (B) assessment (issue 5 of the present decision) and of the toxicity (T) assessment (issues 2 and 3 of the present decision) before deciding whether it is necessary to perform a simulation study. You agreed to perform the requested simulation test if the substance was determined to have a high bioaccumulation potential. ECHA notes that persistence (P) is generally to be assessed before bioaccumulation (B) in order to minimise animal testing. However, ECHA further notes that you have proposed to re-assess the bioaccumulation potential of the substance by performing a new experimental study for log Kow, which does not involve animal testing. ECHA agrees that you may be able to adapt the information requirement for the requested simulation test if you can demonstrate that the substance does not pose PBT/vPvB concerns.

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: Aerobic mineralisation in surface water – simulation biodegradation test (test method: EU C.25./OECD TG 309).

Notes for your consideration

Before conducting the requested test you are advised to consult the ECHA Guidance on information requirements and chemical safety assessment, Chapter R7b, Sections R.7.9.4 and R.7.9.6 and Chapter R.11, on PBT/vPvB assessment. In accordance with Annex I, Section 4, of the REACH Regulation you should then revise the PBT/vPvB assessment when the results of the test detailed above are available.

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

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

"Bioaccumulation in aquatic species, preferably fish" is a standard information requirement as laid down in Annex IX, Section 9.3.2.of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have sought to adapt this information requirement by using (Q)SAR predictions.

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests, "*provided that the conditions set out in Annex XI are met*". This annex proposes some general rules for adapting the standard information requirements set out in Annexes VII to X of the REACH Regulation. In particular, Annex XI, Section 1.3. of the REACH Regulation introduces the concept of Qualitative or Quantitative Structure-Activity Relationship ((Q)SAR) as a possible general rule for adapting the standard information requirements set out in Annexes VII to X of the REACH Regulation.

However, ECHA notes that the (Q)SAR predictions presented in your dossier are highly variable and therefore any conclusion with regard to the bioaccumulation potential of the registered substance is uncertain:

- For your chemical safety assessment, you have chosen to use a BCF of 275.4. This BCF value was calculated with the EPISuite model using a log Kow value of 4.2. This log Kow value of 4.2 was itself calculated with EPISuite.

- You also reported in IUCLID additional information from the literature (Wentsel et al. 1979)[2]. These authors proposed two methods for calculating the log Kow for ethyl centralite based on data available on similar compounds. Log Kow values of 4.37 and 5.88 were calculated and the corresponding BCF values were further calculated resulting in BCF values of 1250 and 17300.

The log Kow value can be used as screening information for assessing the bioaccumulation potential of the substance. For example, in the ECHA Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.11 on PBT/vPvB assessment, a screening criterion has been established for the bioaccumulation assessment, which is log Kow greater than 4.5. However, ECHA notes that the log Kow value for the substance is itself uncertain. You have used a log Kow value of 4.2 predicted by the EPISuite model whereas [redacted] (1979) presented log Kow values ranging from 4.37 to 5.88. In addition, you presented log Kow values back-calculated from experimental log Koc values: the corresponding calculated log Kow values vary between 1.98 and 3.35. No experimental data is available for the log Kow of the registered substance.

ECHA considers that the log Kow of the substance is uncertain and therefore that the QSAR results you have provided to assess the bioaccumulation of the substance and which are based on log Kow are not reliable. ECHA further notes that the log Kow of the substance potentially exceeds the screening criterion of 4.5 established for the PBT/vPvB assessment and therefore that the substance is potentially bioaccumulative or even very bioaccumulative.

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.

[2] [redacted]. 1979a. Problem definition study on TAX (1-acetylhexahydro-3,5-dinitro-1,3,5-triazine), SEX (1-acetyloctahydro-3,5,7-trinitro-1,3,5,7-tetrazine), lead salicylate and lead beta-resorcylate, 2-nitrodiphenylamine and ethyl centralite. Final Report (ADA099749). [redacted]

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7c* bioaccumulation in fish: aqueous and dietary exposure (test method OECD TG 305) is the preferred test to cover the standard information requirement of Annex IX, Section 9.3.2. ECHA Guidance defines further that results obtained from a test with aqueous exposure can be used directly for comparison with the B and vB criteria of Annex XIII of the REACH Regulation and can be used for hazard classification and risk assessment. Comparing the results of a dietary study with the REACH Annex XIII B and vB criteria is more complex and has higher uncertainty. Therefore, the aqueous route of exposure is the preferred route and shall be used whenever technically feasible. If you decide to conduct the study using the dietary exposure route, you shall provide scientifically valid justification for your decision. You shall also attempt to estimate the corresponding BCF value from the dietary test data by using the approaches given in Annex 8 of the OECD TG 305. In any case, you shall report all data derived from the dietary test as listed in the OECD TG 305.

In your comments following the procedure set out in Article 50(1) of the REACH Regulation, you have proposed to derive a more reliable log Kow value in order to infer the bioaccumulation potential of the registered substance. ECHA agrees that you may be able to adapt the information requirement for bioaccumulation if you provide a valid log Kow value that shows that the substance has a low potential for bioaccumulation.

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: Bioaccumulation in fish: aqueous or dietary bioaccumulation fish test (test method: OECD TG 305)

Notes for your consideration

Before conducting the above test you are advised to consult the ECHA *Guidance on information requirements and chemical safety assessment*, Chapter R.11.4. and Figure R.11-4 on the PBT assessment for further information on the integrated testing strategy for the bioaccumulation assessment of the registered substance. In accordance with Annex I, Section 4, of the REACH Regulation you should then revise the PBT/vPvB assessment when the results of the test detailed above are available.

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 01 March 2017.

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

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

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

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

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

Appendix 3: Further information, observations and technical guidance

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

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

3. In carrying out the tests required by the present decision, it is important to ensure that the particular sample of substance tested is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported. If the registration of the substance covers different grades, the sample used for the new tests must be suitable to assess these.

   Furthermore, there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.