EUROPEAN CHEMICALS AGENCY

Helsinki, 10 November 2017

Addressee: [redacted]

Decision number: CCH-D-2114376663-40-01/F
Substance name: Bis(piperidinothiocarbonyl) hexasulphide
EC number: 213-537-2
CAS number: 971-15-3
Registration number: [redacted]
Submission number: [redacted]
Submission date: 29/04/2013
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. **High-pressure liquid chromatogram, gas chromatogram (Annex VI, Section 2.3.6.) of the registered substance;**

   - **Complete chromatogram**

2. ***In vivo* mammalian alkaline comet assay (Annex IX, Section 8.4., column 2; test method: OECD TG 489) in rats, oral route, on the following tissues: liver, glandular stomach and duodenum, with the registered substance;**

   OR

   Transgenic rodent somatic and germ cell gene mutation assays (Annex IX, Section 8.4., column 2; test method: EU B.58/OECD TG 488) in transgenic mice or rats, oral route on the following tissues: liver and glandular stomach, with the registered substance; germ cells and duodenum shall be harvested and stored for up to 5 years. Duodenum shall be analysed if the results of the glandular stomach and of the liver are negative.

3. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats with the registered substance;**

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. **Identification of degradation products (Annex IX, 9.2.3.) using an appropriate test method with the registered substance as further specified in Appendix 1, section 5;**

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

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You may adapt the testing requested above according to the specific rules outlined in Annexes VI to IX 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 **18 May 2020**. You also have to update the chemical safety report, where relevant.

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

Appeal

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

Authorised[1] by Claudio Carlon, Head of Unit, Evaluation E2

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

Appendix 1: Reasons

1. **High-pressure liquid chromatogram, gas chromatogram (Annex VI, Section 2.3.6.)**

In accordance with Article 10(a)(ii) of the REACH Regulation, the technical dossier must contain information on the identity of the substance as specified in Annex VI, Section 2 to the REACH Regulation. In accordance with Annex VI, Section 2 the information provided has to be sufficient to enable the identification of the registered substance.

A high-pressure liquid chromatogram or gas chromatogram is a standard information requirement under Annex VI section 2.3.6. of the REACH Regulation to support the identity of the registered substance.

ECHA notes that you provided in IUCLID Section 1.4. a method description for the chromatographic analysis and a peak list table, however you did not provide the corresponding HPLC chromatogram.

The chromatogram is missing from your dossier and therefore the identity and composition of your substance cannot be verified.

In your comments to the draft decision, you agreed to provide the chromatogram.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation and to Annex VI, 2.3.6., you are requested to provide a HPLC chromatogram in your registration dossier.

As for the reporting in the registration dossier, the information should be included in IUCLID section 1.4.

2. **In vivo mammalian alkaline comet assay (Annex IX, Section 8.4., column 2) or Transgenic rodent somatic and germ cell gene mutation assays (Annex IX, Section 8.4., column 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.

"Mutagenicity" is an information requirement as laid down in Annex VIII, Section 8.4. of the REACH Regulation. Column 2 of Annex IX, Section 8.4. provides that "If there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII and there are no results available from an *in vivo* study already, an appropriate *in vivo* somatic cell genotoxicity study shall be proposed by the Registrant."

The technical dossier contains two *in vitro* gene mutation studies: one in bacteria (5 strains of *Salmonella typhimurium*) performed according to OECD TG 471 with the registered substance that show negative results and one in mammalian cells (L5178Y TK+/- mouse lymphoma cells) performed according to OECD TG 476 with the registered substance that show positive results. The positive results indicate that the substance is inducing gene mutations under the conditions of the tests.

The technical dossier also contains one *in vivo* study (mammalian erythrocyte micronucleus test) performed according to OECD TG 474 with the registered substance that shows negative results.

ECHA notes that you adapted the *in vitro* requirement of Annex VIII, section 8.4.2., using the following justification: "*An* in vitro *mammalian cell gene mutation test in L5178Y TK+/- mouse lymphoma cells was positive with a majority of small colonies that suggests that DPTH* [the registered substance] *could be a clastogen substance. Thus it was more relevant to perform an* in vivo *micronucleus test instead of an* in vitro *test to confirm these results. Finally no* in vitro *chromosome aberration test must be performed.*"

ECHA agrees that the results of the mouse lymphoma assay in the registration dossier show a tendency of larger proportion of small colonies in some of the examined wells.
ECHA further agrees that an induction of slow growing mutants may be associated with substances that induce gross structural changes at the chromosomal level. However, this cannot be considered as definite indication that only aberrations and not point mutations occur.

According to the ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, section R.7.7.3.1, ECHA considers that the *in vivo* mammalian erythrocyte micronucleus study (which you provided) is appropriate to assess structural and numerical chromosome aberrations, but it is not appropriate to assess gene mutations.

Hence, ECHA concludes that the test provided was not appropriate to follow-up positive result in an *in vitro* genotoxicity study for gene mutations, and notes that such an appropriate *in vivo* genotoxicity study is not available for the registered substance.

In your comments to the draft decision, you propose to perform an *in vitro* mammalian gene mutation test (OECD 476). ECHA considers that the positive result seen in the OECD 490 cannot be concluded to be due to clastogenic effect only. Indeed, although there is an increase in small colonies with increasing dose, from the colony counts it can be seen that there is also an increase in the large colony count, which is not consistent with an exclusive clastogenic effect.

Based on your assessment on the toxicokinetics, absorption will be low: "*Based on chemical and physical data, no absorption of DPTH is expected in animals after an oral, dermal or inhalation exposure.*" This could cause concerns about whether the negative result of the OECD TG 474 was because the substance did not reach the bone marrow. However, as the OECD TG 474 test was conducted using intraperitoneal administration, there is no doubt that exposure occurred. Concerning performing an OECD 476 assay, ECHA considers that you are free to perform any *in vitro* investigations you might think to be helpful in choosing a further testing strategy.

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

According to the ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, section R.7.7.6.3, the transgenic rodent somatic and germ cell gene mutation assays ("TGR assay", OECD TG 488) and the *in vivo* mammalian alkaline comet assay ("comet assay", OECD TG 489) are suitable to follow up a positive *in vitro* result on gene mutation.
Hence, ECHA considers that the TGR and the comet assay are suitable tests to follow up the concern on gene mutation for the substance subject to the decision.

In case you decide to perform the TGR assay according to the test method EU B.58/ OECD TG 488, the test shall be performed in transgenic mice or rats and the substance is to be administered orally.

In case you decide to perform the comet assay according to the test method OECD TG 489, the test shall be performed in rats. Having considered the anticipated routes of human exposure and adequate exposure of the target tissue(s) performance of the test by the oral route is appropriate.

In case you decide to perform a TGR assay according to the test method EU B.58/ OECD TG 488, the test shall be performed by analysing tissues from liver as slowly proliferating tissue and primary site of xenobiotic metabolism, glandular stomach and duodenum as rapidly proliferating tissue and site of direct contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the substance, and probable different local absorption rates of the substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to sample both tissues to ensure a sufficient evaluation of the potential for mutagenicity at the site of contact in the gastro-intestinal tract. However, duodenum shall be analysed if the results of the glandular stomach and of the liver are negative.

Male germ cells shall be collected at the same time as the other tissues (liver and glandular stomach), and stored up to 5 years (at or below −70 ºC). This duration is sufficient to allow the Registrant or ECHA, in accordance to Annex IX, Section 8.4., column 2, to decide on the need for assessment of mutation frequency in the collected germ cells.

In case you decide to perform a comet assay according to the test method OECD TG 489, the test shall be performed by analysing tissues from liver as primary site of xenobiotic metabolism, glandular stomach and duodenum as sites of contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the substance, and probable different local absorption rates of the substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to sample both digestive tissues to ensure a sufficient evaluation of the potential for genotoxicity at the site of contact in the gastro-intestinal tract.

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

> Transgenic rodent somatic and germ cell gene mutation assays (test method: EU B.58/ OECD TG 488) in transgenic mice or rats, by oral route on the following tissues: liver and glandular stomach; germ cells and duodenum shall be harvested and stored for up to 5 years; duodenum shall be analysed if the results of the glandular stomach and of the liver are negative.
> OR
> *In vivo* mammalian alkaline comet assay (test method: OECD TG 489) in rats, by oral route, on the following tissues: liver, glandular stomach and duodenum,

Notes for your consideration

You are reminded that according to Annex IX Section 8.4., column 2 of the REACH Regulation, if positive results from an *in vivo* somatic cell study are available, "the potential for germ cell mutagenicity should be considered on the basis of all available data, including toxicokinetic evidence. If no clear conclusions about germ cell mutagenicity can be made, additional investigations shall be considered".

In case you decide to perform the TGR assay, you may consider collecting (see OECD TG 488, paragraph 33) and storing male germ cells for potential further analysis of germ cell mutagenicity in case positive result(s) are obtained from the somatic cells.

In case you decide to perform the comet assay, you may consider examining gonadal cells in addition to the other aforementioned tissues, as it would optimise the use of animals. ECHA notes that a positive result in whole gonads is not necessarily reflective of germ cell damage since gonads contain a mixture of somatic and germ cells. However, such positive result would indicate that the substance and/or its metabolite(s) have reached the gonads and caused genotoxic effects. This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

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

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

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

In the technical dossier you have provided a study record for a "repeated dose 28-day oral toxicity study" (test method: OECD TG 407). However, this study does not provide the information required by Annex IX, Section 8.6.2., because exposure duration is less than 90 days and the number of animals per dose group is significantly lower. Therefore, the sensitivity of a 28-day study is much lower than that of a 90-day study.

You have sought to adapt this information requirement according to Annex IX, Section 8.6.2., column 2. You provided the following justification for the adaptation: *"Study scientifically not necessary / No systemic effect at 1000 mg/kg was observed in the 28-day study performed on rats by oral route. Therefore, a 90-day study is not proposed in this dossier because no systemic effects were expected after 3 months of exposure."* 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 IX, Section 8.6.2., column 2.

You have reported, in section 7.1 of the IUCLID dossier that *"no absorption of DPTH is expected in animals after an oral, dermal or inhalation exposure. DPTH is a highly lipophilic compound (log Kow >4), and poorly soluble in water (< 1 mg/L), therefore DPTH could be poorly absorbed by oral route and by inhalation.*
This assumption is confirmed in the experimental data. In the acute oral toxicity study, no death or clinical signs were observed after administration of 2000 mg/kg bw to rats. And in the inhatation acute study, no mortality was observed in rats treated with 2.83 mg/L (the maximum attainable concentration).

DPTH has water solubility below 1 mg/L, dermal uptake is likely to be low. And with a log Kow higher than 6, the rate of transfer between corneum and the epidermis will be slow and will limit absorption across the skin. Uptake into the stratum corneum itself may be slow. This assumption of a dermal absorption is confirmed by the acute dermal toxicity study (no death or clinical sign at 2000 mg/kg bw in rats) and skin sensitisation data (DPTH showed a negative result in LLNA assay). [As] No absorption of DPTH is expected, therefore no distribution, metabolism or excretion are expected."

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 8.6.2., column 2 because (i) the available repeated short-term toxicity study (28 days) is not showing severe toxicity effects according to the criteria for classifying the substance as R48; (ii) no chronic toxicity study is available; (iii) no information about the substance undergoing immediate disintegration is provided in the registration dossier; (iv) the substance cannot be claimed as being "*unreactive, insoluble and not inhalable*" as there is presence of some systemic effects after oral exposure.

Hence it is anticipated that the registered substances will be available after oral administration, supporting further investigation via the oral route.

In your comments to the draft decision you reiterate the use of low toxicity as a reason to adapt this information requirement. As explained above, ECHA considers that the column 2 conditions of REACH Annex IX 8.6.2. to adapt the information requirement of sub-chronic toxicity study (90-day) are not met. A "low (sub)acute toxicity profile" is not an applicable reason for adapting this study. Moreover, the second criterion for "low (sub)acute toxicity profile" does not seem to be fulfilled as there is a positive OECD Guideline 490 (*In Vitro* Mammalian Cell Gene Mutation Test) which indicates the substance has mutagenic and clastogenic properties.

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.

ECHA has evaluated the most appropriate route of administration for the study.

Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration.

More specifically, even though the information suggests that human exposure to the registered substance by the inhalation route may be likely, some systemic effects after oral treatment were observed in the lung (present of minimal alveolar foamy macrophages), and require further evaluation in a repeated dose toxicity by the oral route. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method EU B.26./OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats.

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.

You have sought to adapt this information requirement according to Annex IX, Section 9.2., column 2. You provided the following justification for the adaptation:

"Further biotic degradation testing shall be proposed by the registrant if the chemical safety assessment according to Annex I indicates the need to investigate further the degradation of the substance and its degradation products. The choice of the appropriate test(s) depends on the results of the chemical safety assessment and may include simulation testing in appropriate media (e.g. water, sediment or soil).

As the chemical safety assessment is not yet performed due to lack of toxicity up to the water solubility limit (EPM method not realisable), no simulation test is proposed."

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Column 2 of Annex IX, Sections 9.2 and 9.2.1.2 because the fact that the chemical safety assessment has not been performed does not represent a valid reason to omit the standard information requirement for simulation testing on ultimate degradation in water. The absence of the chemical safety assessment cannot be regarded as an indication that there is no concern for this endpoint.

Furthermore, according to Annex IX, Section 9.2.1.2, column 2 of the REACH Regulation, simulation testing on ultimate degradation in surface water does not need to be conducted if the substance is highly insoluble in water or is readily biodegradable. ECHA notes that based on the information in the technical dossier, the registered substance is not readily biodegradable in the OECD 301F – biodegradation 0% and has a water solubility of 10.5 ug/L (substance is within the range of concentrations typically used to perform OECD 309 (1 and 100 µg/L)).

Given the lack of degradation in the ready biodegradability study (0%) and the bioaccumulation potential (log Kow = 6.2), ECHA considers that the information is needed for the PBT/vPvB assessment and for the identification of the degradation products in relation to the PBT/vPvB assessment.

You acknowledge this yourself in your PBT assessment by stating "*the lack of biodegradation does not mean that dipentamethylene thiurame hexasulphide is recalcitrant in nature because the stringency of the test procedures could account for the recalcitrance in the ready biodegradability test. Thus, further test should be performed in order to conclude on P assessment.* ***Conclusion on P / vP properties:*** *No conclusion can be reached based on available information*".

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

In your comments to the draft decision, you have expressed your agreement that the PBT/vPvB assessment would need further investigations.

You claim that you have new evidence, which strongly suggest that DPTH and its degradation products are not PBT/vPVB. However, some additional work is needed to confirm this assumption. You propose an alternative and less expensive approach than testing degradation in surface water according to OECD TG 309. According to you the OECD 309 and 305 studies, as well as the use of vertebrates animals, could be avoided if you manage to demonstrate, by a less costly strategy – conducting a degradation assay in water (at 12 Degrees Celsius, pH =7) based on an adaptation of the OECD 111 study, that DPTH and its degradation products are not PBT/vPvB.

You conclude that, if this approach does not rule out PBT/vPvB for DPTH, then OECD 309 tests will be conducted.

ECHA acknowledges your agreement that PBT/vPvB assessment would need further investigations. ECHA agrees that according to REACH, Weight of Evidence approach can be used to fulfil the data gap. ECHA supports your conclusion that if your proposed approach does not rule out the concern of PBT/vPvB for DPTH, then OECD 309 tests needs to be conducted.

ECHA would like to stress that additional evidence is needed to examine whether the fate properties of the substance would cause attenuation of the hydrolysis rate in sediment or soil, or whether DOC would similarly affect the rate in aquatic media such as river or seawater. Additional studies, e.g. examining the influence of dissolved organic carbon / adsorption processes on hydrolysis rates, may be necessary for this. The degradation half-lives obtained in a hydrolysis test cannot on its own be compared to the persistence criteria of Annex XIII (i.e. a substance fulfils the P(vP) criterion if T1/2> 40 (60) days) (ECHA Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT/vPvB assessment (version 3.0, June 2017)[2]. As abiotic degradation is primary degradation, careful consideration will need to be given to the potential formation of stable degradation products with PBT/vPvB properties. Hydrolysis products should be identified in accordance with the recommendations contained in the test guidelines (e.g. OECD TG 111).

ECHA Guidance on Information Requirements and Chemical Safety Assessment Chapter R.11: PBT/vPvB assessment (version 3.0, June 2017) states that hydrolysis may proceed effectively in aquatic, sediment and soil compartments, but it is noted that there are substances reaching rapid hydrolysis rates which are well known to be persistent in soil and/or sediment, e.g. endosulfan[3,4]. Therefore, rapid hydrolysis rates cannot alone lead to concluding that a substance is not persistent. Test results showing rapid hydrolysis rates always need to be evaluated carefully in context with other information on the substance, such as partitioning and ionogenic properties both of which may significantly influence the extent and strength of sorption to soil and sediment. Hydrolysis also needs to be consistently rapid across the range of environmentally relevant pH. To provide confidence in the hydrolysis results, analytical data identifying metabolites to provide a mass balance are also needed. These both demonstrate that primary degradation has occurred, and allow subsequent PBT assessment of the degradants.

[2] The draft decision based on your comments contained an erroneous reference to the guidance, which has been corrected to clarify that the hydrolysis result cannot directly be compared to the P criteria.
[3] UNEP/POPS/POPRC.5/3, July 2009: *"Draft risk profile: endosulfan";*
[4] OSPAR Commission 2002 (ISBN 0 946956 98 7), Hazardous Substances Series: Endosulphan

There is currently no cut off for hydrolysis rate, which could alone be used as justification to conclude that a substance is not persistent. Hydrolysis data always need to be considered in connection with the other properties, such as partitioning properties and the knowledge on the abiotic and biotic degradation pathways.

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* (version 4.0, June 2017) 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 (version 4.0, June 2017) 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.

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) at the temperature of 12°C.

Notes for your consideration

In accordance with Annex I, Section 4, of the REACH Regulation you should revise the PBT assessment when results of the test detailed above are available. You are also advised to consult the ECHA Guidance on information requirements and chemical safety assessment Chapter R.11, Section R.11.4.1.1. and Figure R. 11-3 on PBT assessment for the integrated testing strategy for persistency assessment in particular taking into account the degradation products of the registered substance.

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

The identification of the degradation products is a standard information requirement according to column 1, Section 9.2.3. of Annex IX of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

The biodegradation section in the technical dossier does not contain any information in relation to 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.

According to Annex IX, Section 9.2.3., column 2 of the REACH Regulation, identification of degradation products is not needed if the substance is readily biodegradable. ECHA notes that based on the information in the technical dossier, the registered substance is not readily biodegradable (based on OECD Guideline 301 F, 0% O2 consumption was observed after 28 days) as also discussed under request 4 above.

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

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

In summary, ECHA notes that you have not provided any justification in your chemical safety assessment (CSA) or in the technical dossier for why there is no need to provide information on the degradation products. ECHA considers that this information is needed in relation to the PBT/vPvB assessment and risk assessment.
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.

Regarding appropriate and suitable test method, the methods will have to be substance-specific. When analytically possible, identification, stability, behaviour, molar quantity of metabolites relative to the parent compound should be evaluated. In addition, degradation half-life, log Kow and potential toxicity of the metabolite may be investigated. You may obtain this information from the degradation study also requested in this decision, or by some other measure. You will need to provide a scientifically valid justification for the chosen method.

In your comments to the Proposal for Amendment submitted by a Member States Competent Authority, you brought forward several arguments against this request, mainly referring to issues already addressed under request 4 above. In addition, you indicate that due to the low water solubility of the registered substance, the identification of degradation products in the OECD 309 TG will be technically not feasible. With the present request, ECHA has simply formalised the aforementioned issues in a separate request to clarify that information on biotic and abiotic degradation can be obtained from the degradation study also requested in this decision, or by some other measure, such as the modified OECD 111 that you proposed in your comments to the draft decision and confirmed in your comments to the proposal for amendment. In case you decide to identify the degradation products as a part of the OECD TG 309, a solvent may be used to facilitate the identification of the degradation products. The use of solvent is not a preferred option for the kinetic part of the study which should be conducted with a concentration below the water solubility. Use of solvent in degradation studies is discussed in ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Section R.7.9.4.1. and in the OECD TG 309.

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:

Identification of the degradation products (Annex IX, Section 9.2.3.) by using an appropriate and suitable test method, as explained above in this section.

Notes for your consideration

Before providing the above information you are advised to consult the ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R.7b., Sections R.7.9.2.3 and R.7.9.4. These guidance documents explain that the data on degradation products is only required if information on the degradation products following primary degradation is required in order to complete the chemical safety assessment. Section R.7.9.4. further states that when substance is not fully degraded or mineralised, degradation products may be determined by chemical analysis.

6. 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 according to Annex XI, Section 1.3 governing Qualitative or Quantitative structure-activity relationship (QSAR). You provided QSAR calculation as an adaptation for this endpoint:

"The bioconcentration factor (BCF) of dipentamethylene thiurame hexasulphide was evaluated with BCFBAF model v3.01 from EPI Suite v4.1, which fulfilled all OECD principles. Test substance is within the domain of the BCFBAF model based on the molecular weight and fragments present in the BCFBAF database."

You have also claimed to have attached the QMRF and QPRF.

However, ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI; Section 1.3 because the substance does not fall within the applicability domain of the (Q)SAR model and adequate and reliable documentation (QMRF and QPRF) of the applied method were in fact not provided in the registration dossier.

More specifically, the registered substance has more occurrences of the fragment disulphide than those allowed to fall within the applicability domain of Meylan model for BCF (i.e., three, while only a maximum of two are allowed). This affects the reliability of the prediction.

The correction fragment used in the BCFBAF v3.01 calculation for DPTH contains experimental data for an analogue similar substance, CAS# 120-54-7. The experimental LogKow of CAS# 120-54-7 is 2.8. Based on the experimental data provided by you the LogKow of the registered substance might be as high as 6.2, therefore the comparison between registered substance and CAS# 120-54-7 seems inadequate regarding bioaccumulation.

As an additional note, ECHA considers the LogKow value of 6.2 from GLP HPLC study (reliability 3, disregarded by you due to deficiencies with the reference substances used in the test) as adequate. You have flagged it as unreliable due to the result being much higher than the predicted value (4.43). ECHA considers the predicted value to be unreliable because the structure falls outside the applicability domain of the model (the fragments of the molecule are not sufficiently covered by the training set of the model), and calculations for similar molecules are unreliable. Consequently, ECHA considers the results of the available HPLC test to be adequate despite the noted deficiencies with the reference substances used in the test.

ECHA notes that even if the LogKow value (6.2) would have been used, the prediction with the Meylan model would still not be reliable because of the occurrences of the disulphide fragment. Therefore because of not having sufficiently covered the fragments of the target substance, the BCF prediction cannot be accepted.

According to REACH requirement Annex IX, Section 9.3.2 and Annex XI, Section 1.3, the endpoint requirements are not fulfilled.

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

In your comments to the draft decision, you have expressed your agreement that the PBT/vPvB assessment would need further investigations.

You claim that you have new evidence, which strongly suggests that DPTH and its degradation products are not PBT/vPVB. However, some additional work is needed to confirm this assumption. You propose an alternative and less expensive approach than studying bioaccumulation of DPTH in fish according to OECD 305 TG. According to you the OECD 309 and 305 studies, as well as the use of vertebrates animals, could be avoided if you manage to demonstrate, by a less costly strategy – conducting a degradation assay in water (at 12 Degrees Celsius, pH =7) based on an adaptation of the OECD 111 study, that DPTH and its degradation products are not PBT/vPvB.

You have also stated that the potential hydrolysis products have low bioaccumulation potential and have referred to a bioaccumulation study with DPT4 (CAS 120-54-7) which resulted in a BCF of <32L/Kg in fish. You argue that other potential hydrolysis products such as DPT1, DPT2, DPT3 and DPT4 are unlikely to be PBT as they are smaller molecules than DPT4. You point out that there is no data available for DPT5 and DPT6 so uncertainties may remain as to their bioaccumulation potential but you argue that bioaccumulation potential is likely to be low given the low solubility of DPTH in octanol (0.044 mmol/L).

You conclude that if the conduct of the proposed degradation assay in water does not rule out PBT/vPvB for DPTH, and the OECD 309 does not rule out PBT/vPvB for DPTH either, then an OECD 305 test will be conducted.

ECHA acknowledges your agreement that PBT/vPvB assessment would need further investigations. ECHA agrees that according to REACH, a Weight of Evidence approach in accordance with Annex XI can be used to fulfil the data gap and to complete the PBT assessment but notes that all of the degradation products need to be carefully considered and robust evidence of low bioaccumulation should be presented for all of the degradation products. All of the above and that which is outlined in section 4 above, needs to be considered by you in your testing strategy. ECHA understands that if your proposed approach does not rule out a PBT/vPvB concern for DPTH, then OECD 305 tests will be conducted.

As explained above in section 4 of this decision, please note ECHA's considerations that hydrolysis data always need to be considered in connection with the other properties, such as partitioning properties and the knowledge on the abiotic and biotic degradation pathways.

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

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7c* (version 3.0, June 2017) bioaccumulation in fish: aqueous and dietary exposure (test method EU C.13. / 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 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 decided 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 305 TG. In any case you shall report all data derived from the dietary test as listed in the OECD 305 TG.

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 and dietary exposure OECD TG 305-I, by aqueous exposure.

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. You should revise the PBT assessment when information on bioaccumulation is available.

Deadline in the decision

In your comments on the draft decision you have requested an extension to the deadline in the decision from 18 to 30 months. You argue that the registered substance is a substance that can be considered a *"difficult-to-test"* substance and that additional time is needed for the analytical work and carrying out the tests.

ECHA agrees that this substance is a difficult to test substance and there might be a need for sequential testing. Consequently, additional time is granted and the deadline in the draft decision is amended from 18 to 30 months.

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 12 January 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 request(s).

ECHA took into account your comments and amended the deadline.

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

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

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

ECHA referred the draft decision to the Member State Committee.

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

In addition, you provided comments on the draft decision. These comments were not taken into account by the Member State Committee as they were considered to be outside of the scope of Article 51(5).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-56 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

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

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

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

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

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