~~Confidential~~

Helsinki, 17 November 2021

Addressees
Registrant of DPTU_Joint_Submission listed in the last Appendix of this decision

Date of submission of the dossier subject of a decision
18/12/2020

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: 1,3-diphenyl-2-thiourea
EC number: 203-004-2
CAS number: 102-08-9

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

DECISION ON TESTING PROPOSAL(S)

Based on Article 40 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by ***24 November 2022***.

The requested information must be generated using the Substance unless otherwise specified.

Information required from the Registrants subject to Annex IX of REACH

1. 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, oral: glandular stomach and duodenum.

2. Long-term toxicity testing on terrestrial invertebrates (Annex X, Section 9.4.4.; test method: EU C.33/OECD TG 222 or EU C.32/OECD TG 220 or EU C.39/OECD TG 232)

3. Effects on soil micro-organisms (Annex IX, Section 9.4.2.; test method: EU C.21./OECD TG 216).

Reasons for the request(s) are explained in the Appendix entitled "Reasons to request information required under Annex IX of REACH".

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". For references used in this decision, please consult the Appendix entitled "List of references".

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.

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 IX of REACH

This decision is based on the examination of the testing proposals you submitted.

1. In vivo mammalian alkaline comet assay

An appropriate *in vivo* somatic cell genotoxicity is an information requirement under Annex IX to REACH (Section 8.4., Column 2) if (1) there is a positive result in any of the *in vitro* genotoxicity study under Annex VII or VIII to REACH and (2) there are no results available from an *in vivo* study.

Your dossier contains positive results for the *in vitro* gene mutation study in mammalian cells (OECD TG 476; [redacted], 2012) which raise the concern for gene mutations. In the dossier there are negative results available from an *in vivo* mammalian erythrocyte micronucleus test (OECD TG 474; [redacted] 2012). However, this study does not address the concern on gene mutations.

1.1. Information provided to fulfil the information requirement

You submitted a testing proposal for an *In vivo* mammalian alkaline comet assay to be performed with the Substance.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Genetic toxicity *in vivo*. You provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

ECHA agrees that an appropriate *in vivo* follow up genotoxicity study is necessary to address the gene mutation concern identified *in vitro.*

1.2. Test selection

According to the ECHA Guidance Chapter R.7, Section R.7.7.6.3 the *in vivo* mammalian alkaline comet assay ("comet assay", OECD TG 489) is suitable to follow up a positive *in vitro* result on gene mutation.

1.3. Specification of the study design

You proposed testing in the rat. According to the test method OECD TG 489, the test must be performed in rats.

You proposed testing by the oral route. 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 line with the test method OECD TG 489, the test must 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 analyse both tissues to ensure a sufficient evaluation of the potential for genotoxicity at the site of contact in the gastro-intestinal tract.

Germ cells

A subsequent germ cell genotoxicity study (TGR/OECD TG 488, or CA on spermatogonia/OECD TG 483) may still be required under Annex IX of REACH, in case 1) an *in vivo* genotoxicity test on somatic cell is positive, and 2) no clear conclusion can be made on germ cell mutagenicity.

Therefore, you may consider to collect the male gonadal cells collected from the seminiferous tubules in addition to the other aforementioned tissues in the comet assay, as it would optimise the use of animals. You can prepare the slides for male gonadal cells and store them for up to 2 months, at room temperature, in dry conditions and protected from light. Following the generation and analysis of data on somatic cells in the comet assay, in accordance to Annex IX, Section 8.4., column 2, you should consider analysing the slides prepared with gonadal cells. 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.

1.4. Outcome

Your testing proposal is accepted under Article 40(3)(a) and you are requested to conduct the test with the Substance, as specified above.

In your comments on the draft decision, you agree to conduct the study and to provide this information through a dossier update by the expected deadline.

2. Long-term toxicity testing on terrestrial invertebrates

Short-term toxicity to invertebrates is an information requirement under Annex IX to REACH (Section 9.4.1). Long-term toxicity testing must be considered (Section 9.4., column 2) if the substance has a high potential to adsorb to soil or is very persistent.

ECHA Guidance R.7.11.5.3. clarifies that a substance is considered to be very persistent in soil if it has a half-life >180 days. In the absence of specific soil data, high persistence is assumed unless the substance is readily biodegradable.

Under Section 5.2.1. of your technical dossier, you report 0% degradation after 28 days based on OECD TG 301F. Your technical dossier does not include any specific soil biodegradation data.

Based on the above, the Substance is concluded to be potentially highly persistent in soil. Therefore, information on long-term toxicity on terrestrial organisms must be provided.

Under Article 40(3)(c) of REACH, ECHA may require a registrant to carry out one or more additional tests in case of non-compliance of the testing proposal with Annexes IX, X or XI of the REACH Regulation. The information requirement on Effects on terrestrial organisms at Annex IX covers short-term toxicity on invertebrates (Section 9.4.1.) and on plants (Section 9.4.3.) and effects on soil micro-organisms (9.4.2.). However, you have not provided a testing proposal for toxicity on terrestrial invertebrates. In case of data gap for toxicity on terrestrial invertebrates, it is necessary to request this information as an additional test to ensure compliance with the endpoint.

2.1. Information provided to fulfil the information requirement

Your registration dossier does not include any information on effects on terrestrial invertebrates.

Instead, you have adapted this information requirement under Annex IX, Section 9.4., column 2 with the following justification: "*The exposure assessment of DPTU (see Chapter 9 of the chemical safety report) based on PNECsoil(screen) does not indicate any risk for terrestrial compartment under any scenario* […]. *However, in accordance with ECHA's guidance* […], *in the absence of data of toxicity to soil organisms for soil hazard category 3 substances as is the case for DPTU (Non-readily biodegradable substance classified as toxic to aquatic life with long lasting effects), confirmatory long-term terrestrial toxicity testing must be carried out. Therefore the registrant proposed to perform an OECD 216 study*."

As specified under Annex IX, Section 9.4., column 2, in the absence of toxicity data to soil organisms, the equilibrium partitioning method (EPM) may be applied to assess the hazard to soil organisms. The choice of the appropriate tests depends on the outcome of the chemical safety assessment.

In this context, ECHA Guidance R.7.11.6. describes an integrated testing strategy (ITS) for soil toxicity, which rely on the assignment of the Substance to a "soil hazard category" and on an initial screening assessment using the EPM, in order to decide the information needed for the chemical safety assessment.

Based on the information from your registration dossier:

- The Substance is not considered to have high adsorption potential to soil (log Kow value of 2 at pH 6 and of 1.51 at pH 12, based on OECD TG 107);
- The Substance is considered to be potentially highly persistent in soils as it not readily biodegradable (0% degradation after 28 days in the OECD TG 301F);
- The Substance is not considered to be very toxic to aquatic organisms as reliable information is available and the lowest short-term EC/LC50 values are > 1 mg/L for all three trophic levels (fish, aquatic invertebrates, and algae).

In addition, you have conducted an initial screening assessment based on a $PNEC_{screen}$ estimated using the EPM and a quantitative exposure assessment for the soil compartment (PEC_{soil}). This screening assessment does not indicate a risk for the soil compartment.

We have assessed your adaptation and identified the following issue:

The information from your dossier indicates that the Substance falls into the soil hazard category 3 (HC3) described in the ITS for soil toxicity. Hence, at least one confirmatory long-term toxicity test must be provided to confirm the outcome of the screening assessment.

ECHA Guidance R.7.11.5.3. specifies that, in the absence of a clear indication of selective toxicity, an invertebrate (earthworm or collembolan) test must be conducted.

Your registration dossier provides the following information:

- a long-term toxicity study on aquatic invertebrates according to OECD TG 211 on the Substance with a 21d-NOEC of 0.15 mg/L;
- a toxicity study to aquatic algae and cyanobacteria according to OECD TG 201 on the Substance with a 72h-ErC10 of 4.7 mg/L;
- a ready biodegradability study according to OECD TG 301F on the Substance. Based on this study you provide a 28d-NOEC of 100 mg/L.

The aquatic toxicity data available in your dossier indicates that invertebrates are more sensitive towards the toxicity of the Substance than plants and micro-organisms. On this basis, the confirmatory long-term toxicity test on terrestrial organisms must be conducted on an invertebrate species (earthworm or collembolan). Therefore, your adaptation is rejected and the information requirement is not fulfilled.

2.2. Test selection and study specifications

The Earthworm Reproduction Test (test method: EU C.33/OECD TG 222), Enchytraeid Reproduction Test (test method: EU C.32/OECD TG 220) and the Collembolan Reproduction Test in Soil (test method: EU C.39/OECD TG 232) are appropriate to cover the information requirement for long-term toxicity on terrestrial invertebrates (ECHA Guidance R.7.11.3.1).

2.3. Outcome

Under Article 40(3)(c), you are therefore requested to conduct the additional test with the Substance, as specified above.

In your comments on the draft decision, you agree to conduct the study and to provide this information through a dossier update by the expected deadline.

3. Effects on soil micro-organisms

Effects on soil microorganisms is an information requirement under Annex IX to REACH (Section 9.4.2).

3.1. Information provided to fulfil the information requirement

You have submitted a testing proposal for a Soil Microorganisms: Nitrogen Transformation Test (test method: EU C.21/OECD TG 216).

Your registration dossier does not include any information on long-term toxicity on soil microorganisms nor any justification as to why the information requirement may be omitted.

Therefore, ECHA agrees that an appropriate study on long-term toxicity testing on soil microorganisms is needed.

3.2. Test selection and study specifications

ECHA Guidance R.7.11.3.1. specifies that the nitrogen transformation test (EU C.21/OECD TG 216) is considered suitable for assessing long-term adverse effects on soil microorganisms for most non-agrochemicals.

3.3. Outcome

Your testing proposal is accepted under Article 40(3)(a) and you are requested to conduct the test with the Substance, as specified above.

In your comments on the draft decision, you agree to conduct the study and to provide this information through a dossier update by the expected deadline.

Appendix B: 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[2].

B. Test material

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 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.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[3].

[2] https://echa.europa.eu/practical-guides
[3] https://echa.europa.eu/manuals

Appendix C: Procedure

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 12 February 2021.

ECHA held a third party consultation for the testing proposal(s) from 18 March 2021 until 3 May 2021. ECHA did not receive information from third parties.

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

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

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request(s).

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix D: List of references - ECHA Guidance[4] 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)[5]

RAAF - considerations on multi-constituent substances and UVCBs (RAAF UVCB, March 2017)[6]

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.

[4] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[5] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[6] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316

OECD Guidance documents[7]
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.

[7] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix E: Addressees of this decision and the corresponding information requirements applicable to them

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.