~~Confidential~~

Helsinki, 05 January 2023

Addressee
Registrant of DBTU_joint submission as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
14/05/2018

Registered substance subject to this decision ("the Substance")
Substance name: 1,3-dibutyl-2-thiourea
EC/List number: 203-674-6

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***13 January 2025***.

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

Information required from all the Registrants subject to Annex VIII of REACH

1. Short-term repeated dose toxicity (28 days) (Annex VIII, Section 8.6.1.; test method: EU B.7./OECD 407) by oral route, in rats

The reasons for the decision are explained in Appendix 1.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressee of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

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 requirements for testing and reporting new tests under REACH, see Appendix 4.

Appeal

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

Failure to comply

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

Authorised[1] under the authority of Mike Rasenberg, Director of Hazard Assessment

Appendix 1: Reasons for the decision
Appendix 2: Procedure
Appendix 3: Addressees of the decision and their individual information requirements
Appendix 4: Conducting and reporting new tests under REACH

[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 for the decision

Contents

Reasons related to the information under Annex VIII of REACH

1. Short-term repeated dose toxicity (28 days)

1 A short-term repeated dose toxicity study (28 days) is an information requirement under Annex VIII, Section 8.6.1.

1.1. Information provided

2 You have adapted this information requirement by using a Grouping of substances and read-across approach and provided the following information with the analogue substance 1,3-diethyl-2-thiourea (EC 203-308-5):

(i) 7-weeks study in rats (1978)

(ii) 7-weeks study in mice (1978)

(iii) Carcinogenicity tests in rats (1978)

(iv) Carcinogenicity tests in mice (1978)

(v) Read-across justification document in IUCLID Section 7.5.1.

3 You provide the following reasoning for the prediction of this information requirement:

4 You explain that both structures differ only in the number of carbons in the chains (4 *versus* 2) and have the same profile of toxicity based on the structural alerts identified with OECD QSAR Toolbox (version 4.0). You also claim that testing with the analogue represents a worst case scenario as: "*1,3-diethyl-2-thiourea (source substance) is smaller and more soluble than 1,3-dibutyl-2-thiourea, so DETU will be more absorbed than DBTU. The read-across proposed betweeen DETU and DBTU is a worst-case scenario. This assumption is confirmed by the acute oral data : the LD50 of DETU is lower than DBTU's value.*". You also state that "*1,3-dibutyl-2-thiourea and 1,3-diethyl-2-thiourea are not irritating to the skin, but skin sensitising*".

5 ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted based on a based on a worst-case approach.

1.2. Assessment of the information provided

6 We have assessed this information and identified the following issue:

1.2.1. *Read-across adaptation rejected*

7 Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group.

8 Additional information on what is necessary when justifying a read-across approach can be found in the Guidance on IRs and CSA, Chapter R.6. and related documents (RAAF, 2017; RAAF UVCB, 2017).

9 We have identified the following issues with the prediction of the toxicological properties:

1.2.1.1. Missing supportive information

10 Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

11 Supporting information must include bridging studies to compare properties of the Substance and the selected source substance to confirm your claimed worst-case prediction.

12 As indicated above, your read-across hypothesis is based on the assumption that the source substance constitutes a worst-case for the prediction of the property under consideration of the Substance. In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substance(s) is necessary to confirm a conservative prediction of the properties of the Substance from the data on the source substance(s). Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and for the source substance(s).

13 You argue that "*In toxicology, the larger substances are considered to be less toxic because their absorption is lower than a small structure"* and conclude on the basis of acute oral studies on the target and source substance that "*For the oral acute toxicity, 1,3-dibutyl-2-thiourea showed mortality (1/6 rats) at the dose of 2000 mg/kg, and 1,3-diethyl-2-thiourea has an oral LD50 of 930 mg/kg. Based on these results, 1,3-diethyl-2-thiourea seems to be more harmful than 1,3-diethyl-2-thiourea*.".

14 ECHA notes that the argument that the size of the carbon chain length is a direct measure for toxicity based on the acute oral studies is not substantiated with toxicological data from a lower and a higher carbon-chain length substance to show a trend in the toxicological properties. Furthermore, as explained under section 1.2.1.2., acute toxicity data are not considered relevant to predict repeated dose toxicity.

15 In the absence of such information, you have not established that the source substance constitutes a worst-case for the prediction of the property under consideration of the Substance. Therefore, you have not provided sufficient supporting information to scientifically justify the read-across.

1.2.1.2. Relevance of the supporting information

16 Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties.

17 According to the Guidance on IRs and CSA, Section R.6.2.2.1.f., "it is important to provide supporting information to strengthen the rationale for the read-across approach. Thus, in addition to the property/endpoint being read across, it is also useful to show that additional properties, relevant to the endpoint, are also (qualitatively or quantitatively) similar between the source and target chemicals".

18 In order to support your claim that the Substance and source substance have similar properties for the endpoints under consideration, you refer to studies relating to the acute toxicity, skin irritation, and skin sensitisation properties of the Substance and the source substance.

19 However, these studies do not inform on the repeated dose toxicity properties of the Substance and of the source substances. Accordingly, this information is not considered as relevant to support your read-across hypothesis and you have not provided supporting information to scientifically justify the read-across explanation for prediction of properties.

1.2.1.3. Adequacy and reliability of the studies on the source substance

20 Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 407. Therefore, the following specifications must be met:

a. at least weekly food consumption measurements.
b. data on functional observations during the fourth exposure week, i.e. sensory activity, grip strength and motor activity assessments;
c. haematological and clinical biochemistry tests as specified in paragraphs 32-39 of the test guideline;
d. terminal organ and body weights;
e. gross pathology, including incidence and severity, as specified in paragraphs 40-46 of the test guideline.
f. full histopathology, including incidence and severity, as specified in paragraphs 47-49 of the test guideline.

21 Your registration dossier provides two studies (i) and (ii) which are 7-weeks dose range finding studies in rat and mice for two carcinogenicity studies listed under (iii) and (iv). The following specifications in these studies are not according to the requirements of the OECD TG 407:

a. data on food consumption are missing in studies (i) to (iv);
b. data on functional observations (nature, severity and duration) are missing in stduies (i) to (iv);
c. data on haematology and clinical biochemistry findings (incidence and severity with relevant base-line values) are missing in studies (i) to (iv);
d. data on terminal organ weights and organ/body weight ratios are missing;
e. data on gross pathology findings (incidence and severity) are missing in studies (i) and (ii);
f. data on histopathology findings (incidence and severity) are missing in studies (i) and (ii).

22 The information provided does not cover the key parameters required by the OECD TG 407.

23 Based on the above, the studies do not provide an adequate and reliable coverage of the key parameters addressed by the OECD TG 407 and these studies are not an adequate basis for your read-across predictions.

1.2.1.4. Conclusion on the read-across approach

24 For the reasons above, you have not established that relevant properties of the Substance can be predicted from data on the source substance(s). Your read-across approach under Annex XI, Section 1.5. is rejected.

25 On this basis, the information requirement is not fulfilled.

1.3. Specification of the study design

26 Following the criteria provided in Annex VIII, Section 8.6.1, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity of the Substance; Guidance on IRs and CSA, Section R.7.5.6.3.1.

27 According to the OECD TG 407, the rat is the preferred species.

28 Therefore, the study must be performed according to the OECD TG 407, in rats and with oral administration of the Substance.

References

The following documents may have been cited in the decision.

Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA)

Chapter R.4 Evaluation of available information; ECHA (2011).
Chapter R.6 QSARs, read-across and grouping; ECHA (2008).
Appendix to Chapter R.6 for nanoforms; ECHA (2019).
Chapter R.7a Endpoint specific guidance, Sections R.7.1 – R.7.7; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Chapter R.7b Endpoint specific guidance, Sections R.7.8 – R.7.9; ECHA (2017).
Appendix to Chapter R.7b for nanomaterials; ECHA (2017).
Chapter R.7c Endpoint specific guidance, Sections R.7.10 – R.7.13; (ECHA 2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Appendix R.7.13-2 Environmental risk assessment for metals and metal compounds; ECHA (2008).
Chapter R.11 PBT/vPvB assessment; ECHA (2017).
Chapter R.16 Environmental exposure assessment; ECHA (2016).

Guidance on data-sharing; ECHA (2017).

All Guidance on REACH is available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

RAAF, 2017 Read-across assessment framework (RAAF), ECHA (2017)
RAAF UVCB, 2017 Read-across assessment framework (RAAF) – considerations on multi- constituent substances and UVCBs), ECHA (2017).

The RAAF and related documents are available online:
https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

***OECD Guidance documents* (OECD GDs)**

OECD GD 23 Guidance document on aquatic toxicity testing of difficult substances and mixtures; No. 23 in the OECD series on testing and assessment, OECD (2019).
OECD GD 29 Guidance document on transformation/dissolution of metals and metal compounds in aqueous media; No. 29 in the OECD series on testing and assessment, OECD (2002).
OECD GD 150 Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption; No. 150 in the OECD series on testing and assessment, OECD (2018).
OECD GD 151 Guidance document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test; No. 151 in the OECD series on testing and assessment, OECD (2013).

Appendix 2: Procedure

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

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

The compliance check was initiated on 07 December 2021.

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

ECHA took into account your comments and modified the requests as follow:

- the request for short term toxicity test to fish (Annex VIII, Section 8.6.1.) has been removed;
- with regard short-term repeated-dose toxicity (Annex VIII, Section 8.6.1.) and as noted by you in your comments on the draft decision, the draft decision erroneously referred to a request for a short-term reapted-dose toxicity study combined with a screening for reproductive/developmental toxicity (OECD TG 422). The request has been modified to a short-term repeated-dose toxicity according to OECD TG 407.

Furthermore, in your comments on the draft decision, you requested an extension of the deadline to provide information from 12 to 24 months from the date of adoption of the decision.

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

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 3: Addressee of this decision and their corresponding information requirements

In accordance with Articles 10(a) and 12(1) of REACH, the information requirements for individual registrations are defined as follows:

- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;

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.

Appendix 4: Conducting and reporting new tests for REACH purposes

1. Requirements when conducting and reporting new tests for REACH purposes

1.1. 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].

(4) Under the introductory part of Annexes VII/VIII/IX/X to REACH, where a test method offers flexibility in the study design, for example in relation to the choice of dose levels or concentrations, the chosen study design must ensure that the data generated are adequate for hazard identification and risk assessment.

1.2. 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 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