EUROPEAN CHEMICALS AGENCY

~~Confidential~~

Helsinki, 02 June 2021

Addressees
Registrants of JS_DBDPEthane listed in the last Appendix of this decision

Date of submission of the dossier subject of a decision
06/06/2019

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: 1,1'-(ethane-1,2-diyl)bis[pentabromobenzene]
EC number: 284-366-9
CAS number: 84852-53-9

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 ***7 June 2024***.

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

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

1. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) by oral route, in rats, specified as follows:
   - Ten weeks premating exposure duration for the parental (P0) generation;
   - Dose level setting shall aim to induce systemic toxicity at the highest dose level;
   - Cohort 1A (Reproductive toxicity);
   - Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation; and
   - Cohorts 2A and 2B (Developmental neurotoxicity).

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

Reasons for the request(s) are explained in the following appendix entitled "Reasons to request information required under Annex X 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 to X to REACH, for registration at more than 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 X of REACH

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

1. Extended one-generation reproductive toxicity study

The basic test design of an extended one-generation reproductive toxicity study (EOGRTS) is a standard information requirement under Annex X to the REACH Regulation. Furthermore, column 2 of Section 8.7.3. defines when the study design needs to be expanded.

1.1. Information provided to fulfil the information requirement

You have submitted a testing proposal for an EOGRTS according to OECD TG 443 with the Substance.

You proposed a tiered testing strategy. First you propose to conduct a toxicokinetic study after repeated exposure in pregnant rats to collect information on the absorption, distribution, and elimination behaviour of the Substance. Should low bioavailability be confirmed in this study, you consider that an EOGRT study may not be needed due to a lack of systemic exposure.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Toxicity to reproduction. 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.

According to Annex X, Section 8.7., Column 2, third indent, the study does not need to be conducted if the following three concomitant criteria are fulfilled: a) the Substance is of low toxicological activity, b) no systemic absorption occurs, and c) there is no or no significant human exposure.

On criterion a), ECHA notes that you have identified neurotoxicity in a recent OECD TG 426 study (see *'Cohorts 2A and 2B'* below).

On criterion b), ECHA notes that the available information indicates poor or negligible absorption. You propose to further clarify this by conducting a toxicokinetic study after repeated exposure in pregnant rats.

On criterion c), ECHA notes that based on the reported uses of the Substance and their associated PROCs it is not possible to establish no or no significant human exposure. In the absence of an exposure assessment demonstrating no or no significant exposure for the uses of the substance, it can be assumed that the following PROCs for example can all lead to significant human exposure; PROC 4: Chemical production where opportunity for exposure arises, PROC 7: Industrial Spraying, PROC 8a: Transfer of substance or mixture at non-dedicated facilities, PROC 10: Roller application and brushing, PROC 11: non industrial spraying. In addition, there are widespread consumer uses of the substance.

Therefore, based on the currently available information, the criteria of 'low toxicological activity', 'no systemic absorption' and 'no or no significant human exposure' are not demonstrated as required in Annex X, Section 8.7., Column 2, third indent.

ECHA agrees that an EOGRTS is necessary. It is at your own discretion to perform the toxicokinetics study and submit an adaptation instead of performing an EOGRTS. Such

adaptation would be assessed in accordance with the follow-up process under Article 42 of REACH.

1.2. Specification of the study design

Species and route selection

You proposed testing by oral route in rats. ECHA agrees with your proposal.

Pre-mating exposure duration and dose-level setting

You proposed ten weeks pre-mating exposure duration. ECHA agrees with your proposal. Ten weeks pre-mating exposure duration is required because there is no substance specific information in the dossier supporting shorter pre-mating exposure duration (ECHA Guidance R.7a, Appendix R.7.6-3).

You propose to base the dose level selection on the existing sub-chronic toxicity study (90-day) and the developmental neurotoxicity study (*'100, 300 and 1000'*) as well as a future toxicokinetics study in pregnant animals, also acknowledging that a separate dose-range finding study may also be needed.

In order to be compliant and not to be rejected due to too low dose levels, the highest dose level must aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects, with the other cohorts being tested at the same dose levels. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

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.

You must provide a justification with your study report that demonstrate that the dose level selection meets the conditions described above.

Cohorts 1A and 1B

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

Cohorts 2A and 2B

Column 2 of Annex X, Section 8.7.3. to REACH provides that the developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity.

You proposed to include Cohort 2A and 2B because a recent developmental neurotoxicity study (OECD TG 426; [redacted] 2018) showed "*morphometric changes in brains of male rats at PND 22 and PND 72 at 100, 320, and 1000 mg/kg/day*". These findings were considered ambiguous as the findings could also be related to the section and measuring methods applied. Because of the ambiguous findings, you propose to include Cohorts 2A and 2B to clarify these effects and their relevance, in particular after a longer exposure duration.

ECHA agrees that there is a particular concern on developmental neurotoxicity based on the morphometric changes observed in brains of male rats in the OECD TG 426 study. ECHA

further notes that the statistical power in the EOGRTS Cohorts 2A/2B is comparable to the OECD TG 426 study.

ECHA agrees that the inclusion of Cohort 2A and 2B are necessary.

1.3. 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.

Further expansion of the study design

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 from other studies or during conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex IX/X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance R.7a, Section R.7.6.

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

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

1. Selection of the Test material(s)

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

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

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

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

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

Appendix C: Procedure

The Substance is listed in the Community rolling action plan (CoRAP) and the substance evaluation started in 2012.

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 28 January 2020.

ECHA held a third party consultation for the testing proposal(s) from 24 February 2020 until 9 April 2020. 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 but amended the deadline.

Timeline for providing the requested information

In your comments on the draft decision, you requested an extension of the deadline to provide information from 24 to 49 months from the date of adoption of the decision. You consider that in addition to the main study, the timeline should also take into account e.g. test substance analysis, a preliminary dose range finding study and adequate reporting. Furthermore, in case that the study needs to be prolonged with the second generation, you request a possibility for an interim dossier update with the request of a prolonged submission date for the final results. With your comments, you provided a statement from a test laboratory.

The statement from the test laboratory estimates a total duration of 125 weeks (31.25 months) for method validation, palatability study, preliminary study and the main study, including reporting. On this basis, ECHA has extended the deadline to 33 months.

Regarding the possibility for an interim dossier update with a request of a prolonged submission date, ECHA notes that after the decision is unanimously agreed by the Member States, ECHA is not in a position to alter the deadline after the decision has been adopted.

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]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[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.