~~Confidential~~

Helsinki, 09 June 2021

Addressees
Registrants of JS_143-29-3 listed in the last Appendix of this decision

Date of submission of the dossier subject of a decision
13/10/2020

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Bis(2-(2-butoxyethoxy)ethoxy)methane
EC number: 205-598-9
CAS number: 143-29-3

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 ***14 September 2023*** *from the date of the decision*.

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

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

1. Extended one-generation reproductive toxicity study also requested below (triggered by Annex IX, Section 8.7.3., column 1)

B. 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 appendices:

- Appendices entitled "Reasons to request information required under Annexes VII to X of REACH", respectively.

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;
- 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.

For certain endpoints, ECHA requests the same study from registrants at different tonnages. In such cases, only the reasoning why the information is required at lower tonnages is provided in the corresponding Appendices. For the tonnage where the study is a standard information requirement, the full reasoning for the request including study design is given. Only one study is to be conducted; the registrants concerned must make every effort to reach an agreement as to who is to carry out the study on behalf of the other registrants under Article 53 of REACH.

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". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations 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 and on scientific information submitted by third parties.

1. Extended one-generation reproductive toxicity study

An extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is an information requirement under Annex IX to REACH (Section 8.7.3.) if the available repeated dose toxicity studies indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity.

Your dossier contains repeated dose toxicity studie(s) which reveal concerns in relation with reproductive toxicity. More specifically, the OECD TG 422 study ([redacted] 2004) shows decreased fertility index, increased incidence of pre-birth loss leading to a decrease in the average number of pups per litter, decreased mean pup weight, and increased pup mortality from day 0 to day 4. The decreased fertility indices and embryo-foetal toxicity were used as a basis for NOAEL setting. Furthermore, in the 'Study proposal additional information' document attached in your testing proposal in IUCLID section 7.8.1, you conclude that "*Based on the previously conducted OECD 422 study, an alert also exists for reproductive toxicity.*"

In your comments you do not agree that an OECD TG 443 study is required at Annex IX. In relation to OECD TG 408, 414 and 422 studies in rats, you consider that *"some findings may be due to material toxicity at a higher dose level and not reproductive toxicity"*, however you do not explain what you mean by 'some findings'. You also consider that if there are no effects concerning reproductive or developmental toxicity in the ongoing OECD TG 414 study in rabbits, the EOGRTS requirement at Annex IX is questionable. Therefore, you ask ECHA to wait until the finalisation of the OECD TG 414 study in rabbits.

ECHA notes that the OECD TG 422 study reported only slight decreases in body weight and body weight gain during the gestation period in the high-dose females when compared to controls. Furthermore, increased liver weights and hepatocellular hypertrophy were reported for the high dose females. You do not explain how these effects (maternal toxicity) would explain the reproductive toxicity effects listed above.

ECHA notes that an OECD TG 414 study does not investigate e.g. fertility or post-natal pup mortality. Therefore, lack of adverse effects in an OECD TG 414 study (in rabbits) does not negate the findings observed in the OECD TG 422 study. Based on the existing OECD TG 422 study, there is a concern in relation with reproductive toxicity.

An EOGRTS is necessary to address the identified concerns in relation with reproductive toxicity.

As explained under request B.1., ECHA agrees that the EOGRT study can be commenced after finalisation of the OECD TG 414 study in rabbits.

For the assessment of the information provided to fulfil the information requirement and the study specifications, see Appendix B, Section 1.

Appendix B: Reasons to request information required under Annex X of REACH

This decision is based on the examination of the testing proposals you submitted and on scientific information submitted by third parties.

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.

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.

ECHA received third party information concerning the testing proposal during the third party consultation.

The third party provided their considerations of the study design and stated that the basic study design (Cohorts 1A and 1B without extension) "*is considered to be appropriate in the absence of any triggers or conditions necessitating the inclusion of additional cohorts or a further generation*". The third party did not provide any further scientifically valid information and studies that would address the relevant substance and hazard endpoint according to Article 40(2) of REACH.

ECHA agrees that an EOGRTS is necessary.

In your comments you agree to perform the study. You consider however that the ongoing OECD TG 414 study in rabbits should be finalised (estimated in March 2021) before commencing the EOGRT study, so that all available information can be considered for the EOGRT study design. ECHA agrees with the proposed timeline.

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 two weeks pre-mating exposure duration. ECHA disagrees 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).

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.

You propose to set the dose levels based on the "*available OECD 422 / OECD 408 study*". ECHA notes that in the OECD TG 422 study with an exposure period of ca. 6 weeks, fertility effects were observed at 800 mg/kg bw/day with only slight maternal toxicity. However, in the OECD TG 408 study with a study duration of 13 weeks, at the high dose level (800 mg/kg bw/day) several cases of premature death occurred, and also several animals were sacrificed due to the severe clinical signs observed. As explained above, the highest dose should be chosen with the aim to induce some systemic toxicity, but not death or severe suffering of the animals. The addition of a fourth test group is often preferable to using a very large interval (e.g. more than a factor of 10) between doses[2].

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

The developmental neurotoxicity Cohorts 2A and 2B must be conducted in case of a particular concern on (developmental) neurotoxicity.

You proposed not to include Cohorts 2A and 2B.

However, existing information on the Substance itself derived from available *in vivo* studies (OECD TG 408, 414 and 422) show evidence of adverse effects on the nervous system at dose levels which are not lethal, or cause severe general toxicity. More specifically, ataxia and/or tremors were observed in these studies in both sexes in the presence of only minor systemic effects (e.g. liver, kidneys), i.e. they are not likely to be secondary to general toxicity. According to ECHA Guidance[3], clinical and/or behavioural signs, not likely to be secondary to general toxicity, indicate a particular concern justifying the inclusion of Cohorts 2A and 2B.

In your comments you consider that the clinical signs such as ataxia and/or tremors observed in the OECD TG 408, 414 and 422 studies did not show a "certain level of severity" which "is not likely to be secondary to general toxicity".

You note that the high dose in the OECD TG 408 study exceeded the maximum tolerated dose, causing mortality, and therefore any clinical signs observed at that dose level are biased by the general toxicity. By extrapolation, you therefore consider that the same dose level should not be considered for the OECD TG 422 study, either.

[2] OECD TG 443, paragraph 23
[3] ECHA Guidance R.7a, Appendix R.7.6-2 EOGRTS Study Design

Within the comments, you provided tabular data on the clinical signs observed in the mid dose of the OECD TG 408 study, concluding that the number of affected animals and days is limited and the slight effects could be attributed to handling of the animals and therefore there is no indication of neurotoxicity reaching a certain level of severity which is not likely to be secondary to general toxicity.

ECHA agrees that there is severe general toxicity observed at the high dose of OECD TG 408 study and the ataxia seen at this dose should not be considered as a specific concern for neurotoxicity. Only minor systemic effects were observed in the mid dose of the OECD TG 408 study. Therefore, the observed ataxia and tremors seen in the mid dose of the OECD TG 408 study are not likely to be secondary to general toxicity. The OECD TG 422 study has a shorter *in vivo* exposure than the OECD TG 408 study, and only minor systemic effects were observed in the high dose of the OECD TG 422 study. Therefore, the observed ataxia and tremors seen in the high dose of the OECD TG 422 study are not likely to be secondary to general toxicity.

According to your tabular data (OECD TG 408, mid dose), all females were affected, showing slight to marked ataxia albeit that the ataxia is not continuously present. The number of affected males, with slight-moderate ataxia, was lower. As all females and some males were affected, ECHA considers that a significant proportion of animals is affected, and the ataxia is caused by treatment of animals with the substance. ECHA considers the ataxia is a functional perturbation of the nervous system and that the ataxia is an adverse effect. Such a finding is sufficient to justify an adverse effect level, and so the ataxia is a serious adverse effect.

In relation to the OECD TG 414 study, you again consider that the ataxia might be connected to general toxicity, such as decreased body weight gain. ECHA notes that the decreased body weight gain, which was 18% in the corrected body weight gain, is not severe general toxicity, and the ataxia observed in most females in the OECD TG 414 study is therefore not likely to be secondary to general toxicity.

For the reasons stated above, the developmental neurotoxicity Cohorts 2A and 2B must be conducted.

1.3. Outcome

Under Article 40(3)(b) your testing proposal is accepted under modified conditions 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 C: 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[4].

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[5].

[4] https://echa.europa.eu/practical-guides
[5] https://echa.europa.eu/manuals

Appendix D: Procedure

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 6 November 2020, following the necessary evaluation of the sub-chronic toxicity study (90-day), requested in compliance check decision number CCH-D-2114470728-37-01/F.

ECHA held a third party consultation for the testing proposal(s) from 26 March 2018 until 11 May 2018. ECHA received information from third parties (see corresponding Appendix).

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.

ECHA took into account your comments and did not amend the request(s).

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) and referred the modified draft decision to the Member State Committee.

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

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-74 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix E: List of references - ECHA Guidance6 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)[7]

RAAF - considerations on multi-constituent substances and UVCBs (RAAF UVCB, March 2017)[7]

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.

OECD Guidance documents[8]

[6] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[7] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[8] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

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.

Appendix F: 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]

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.