EUROPEAN CHEMICALS AGENCY

Helsinki, 7 February 2020

Addressees
Registrants of PFAEO_C12-18_JS listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of a decision
20/05/2019

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Ethanol, 2,2'-iminobis-, N-C12-18-alkyl derivs.
EC number: 276-014-8
CAS number: 71786-60-2

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

DECISION ON A TESTING PROPOSAL

Based on Article 40 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***16 May 2022***.

A. Requirements applicable to all the Registrants subject to Annex IX of REACH

1. The Extended one-generation reproductive toxicity study also requested, and specified, at B.1 below (triggered by Annex IX, Section 8.7.3.).

B. Requirements applicable to all the Registrants subject to Annex X of REACH

1. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route, with the Substance, specified as follows:
   - At least two 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) with extension to mate the Cohort 1B animals to produce the F2 generation which must be followed to weaning; 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.

Conditions to comply with the requests

Each addressee of this decision is bound by the requests for information corresponding to the REACH Annexes applicable to their own registered tonnage of the Substance at the time of evaluation of the jointly submitted dossier.
To identify your legal obligations, please refer to the following:

- you have to comply with the requirements of Annexes VII to IX of REACH, if you have

registered a substance at 100-1000 tpa;

- you have to comply with the requirements of Annexes VII to X of REACH, if you have registered a substance at above 1000 tpa.

Registrants are only required to share the costs of information they are required to submit to fulfil the information requirements for their registration.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

You must submit the information requested in this decision by the deadline indicated above in an updated registration dossier and also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

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 for the requirements applicable to all the Registrants subject to 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 (Annex IX, Section 8.7.3.)**

The basic test design of an extended one-generation reproductive toxicity study (EOGRTS) is a standard information requirement under Annex IX to the REACH Regulation, if the available repeated dose toxicity studies indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. Furthermore, column 2 defines when the study design needs to be expanded.

ECHA considers that concerns in relation with reproductive toxicity are observed in available studies:

- Changes in thyroid histopathology, i.e. hypertrophy of the follicular cells, were observed in both sexes in the OECD TG 408 study with no clear evidence of hepatocyte hypertrophy or liver enzyme induction
- Lower number of corpora lutea and implantation sites, increased post-implantation losses, lower litter sizes, lower live birth index and lower viability index were reported in the OECD TG 422 study.

As the condition of Annex IX, Section 8.7.3. column 1 is fulfilled, an EOGRTS according to OECD TG 443 as specified in this decision is an information requirement for your registration.

For the specifications of the study design see Appendix B.

Appendix B: Reasons for the requirement applicable to all the Registrants subject to 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 (Annex X, Section 8.7.3.)**

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.

You have provided a reference to an earlier decision[2] on a testing proposal for an EOGRTS according to OECD TG 443, and you acknowledge that "*ECHA will confirm final details of study [...] after considerering this updated dossier*." You have provided the following specification of the study design:

- "*extended one-generation reproductive toxicity - basic test design (Cohorts 1A, and 1B without extension)*"
- Test animals: Wistar rat

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.

The proposed study design requires modification to fulfil the information requirement.

The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

ECHA considers that a minimum of 2-week premating exposure duration for P0 animals is required because the full spectrum of parameters on sexual function and fertility will be covered in the F1 animals.

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.

[2] https://echa.europa.eu/documents/10162/920c7f08-595f-2a4e-3cd8-588f8d4a90eb

Extension of Cohort 1B

If the Column 2 conditions of Section 8.7.3., Annex IX/X are met, Cohort 1B must be extended by mating the Cohort 1B animals to produce the F2 generation.

You proposed not to include the extension of Cohort 1B but did not provide any justifications.

However, ECHA considers that the criteria to extend the Cohort 1B are met, because:

- The use of the Substance reported in the joint submission leads to significant exposure of consumers and professionals because the Substance is used by professionals in cleaning and care products and plant protection products (spray applications and direct application (PROCs 4, 8a, 8b, 10, 11, 13) and by consumers in washing and cleaning products, polishes and waxes we well as plant protection products (spray applications, and direct application).

- Furthermore, there are indications for endocrine-disrupting modes of action because changes in thyroid histopathology, i.e. hypertrophy of the follicular cells, were observed in both sexes in the OECD TG 408 study with no clear evidence of hepatocyte hypertrophy or liver enzyme induction.

Therefore, the Cohort 1B must be extended.

The F2 generation must be followed to weaning allowing assessment of nursing and lactation of the F1 parents and postnatal development of F2 offspring. Investigations for F2 pups must be similar to those requested for F1 pups in OECD TG 443 and described in OECD GD 151[3]. It is recommended to aim to 20 litter per dose group in order to have similar statistical power for investigations than in P0 generation.

Cohorts 2A and 2B

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

You proposed not to include Cohorts 2A and 2B but did not provide any justifications.

ECHA notes that existing information on the Substance itself derived from the available OECD TG 408 study shows evidence of thyroid toxicity. Specifically, histopathological changes, i.e. hypertrophy of the follicular cells, was observed in both sexes with no clear evidence of hepatocyte hypertrophy or liver enzyme induction. Signs of thyroid toxicity rise a particular concern on developmental neurotoxicity (ECHA Guidance R.7a).

ECHA concludes that the developmental neurotoxicity cohorts 2A and 2B need to be conducted because there is a particular concern on (developmental) neurotoxicity.

Species and route selection

You proposed testing in Wistar rats. ECHA agrees with your proposal.

[3]http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2013)10&doclanguage=en

You did not specify the route for testing. ECHA considers that the oral route is the most appropriate route of administration, since the Substance to be tested is a liquid.

b) Consideration of the information received during third party consultation

ECHA received information from third parties concerning the testing proposal. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

A third party has suggested that '*the data from 2,2'-iminodiethanol is used in a read-across argumentation'* for the Substance for this information requirement. The third party considers that 2,2'-iminodiethanol ('the source substance') has the same structure as the Substance '*but without the N-alkyl chain*'. According to the third party, an EOGRTS was performed for the proposed source substance, and effects were observed in the developmental neurotoxicity and immunotoxicity cohorts; these data may provide '*a worst-case scenario*' for the Substance.

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 a justification for the read-across including a hypothesis, explanation of the rationale for the prediction of properties and robust study summary(ies) of the source study(ies)[4].

The third party did not provide documentation as to why the information submitted for the source substance is relevant for the Substance.

In the absence of such documentation, ECHA cannot verify that the properties of the Substance can be predicted from the data on the proposed source substance.

c) Outcome

Under Article 40(3)(b) of the REACH Regulation, you are requested to carry out the proposed test under modified conditions, as explained above, with the Substance.

Further expansion of the study design

No triggers for the inclusion of Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including 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[5].

[4] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.6.1
[5] ECHA Guidance R.7a, Section R.7.6.

Appendix C: Procedural history

On 7 April 2017 ECHA issued decision TPE-D-2114356598-33-01/F[2]

On 8 January 2019 the registrants updated the dossier and provided the results of the 90-day sub-chronic toxicity study.

On 21 January 2019 ECHA informed that registrants that the request for an EOGRT study was withdrawn and would be addressed in this separate decision.

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 9 January 2019.

ECHA held a third party consultation for the testing proposal from 25 June 2019 until 9 August 2019. ECHA received information from third parties (see Appendix B).

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of REACH.

The decision making followed the procedure of Articles 50 and 51 of REACH, as described below:

ECHA notified you of the draft decision and invited you to provide comments within 30 days of the notification.

ECHA did not receive any comments within the 30-day notification period.

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: Observations and technical guidance

1. This testing proposal examination decision does not prevent ECHA from initiating compliance checks at a later stage on the registrations present.

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(s).

3. Test guidelines, GLP requirements and reporting

   Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

   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.

   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: 'How to report robust study summaries'[6].

4. Test material

   Selection of the test material(s) for UVCB substances

   The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

   While selecting the test material you must take into account 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. Any constituents that have harmonised classification and labelling according to the CLP Regulation (Regulation (EC) No 1272/2008) must be identified and quantified using the appropriate analytical methods.

   The OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 11 [ENV/MC/CHEM(98)16] requires a careful identification of the test material and description of its characteristics. In addition, the Test Methods Regulation (EU) 440/2008, as amended by Regulation (EU) 2016/266, requires that "*if the test method is used for the testing of a [...] UVCB [...] sufficient information on its composition should be made available, as far as possible, e.g. by the chemical identity of its constituents, their quantitative occurrence, and relevant properties of the constituents*".

[6] https://echa.europa.eu/practical-guides

In order to meet this requirement, all the constituents of the test material used for each test must be identified as far as possible. For each constituent the concentration value in the test material must be reported in the Test material section of the endpoint study record.

Technical Reporting of the test material for UVCB substances

The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers" on the ECHA website7.

5. List of references of the ECHA Guidance and other guidance/ reference documents[8]

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 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)[9]

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.

[7] https://echa.europa.eu/manuals
[8] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[9] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

OECD Guidance documents
Guidance Document on aqueous –phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.
Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No 43, referred to as OECD GD 43.

Appendix E: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fulfilled
[redacted]	[redacted]	[redacted]

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.