

Helsinki, 07 February 2020

Addressees

Registrants of C12-14-alcohol MGE listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision

21 March 2019

Registered substance subject to this decision, hereafter 'the Substance'

Substance name: Oxirane, mono[(C12-14-alkyloxy)methyl] derivs.

EC number: 271-846-8

CAS number: 68609-97-2

Decision number: [Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/D)]**DECISION ON A COMPLIANCE CHECK**Based on Article 41 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 X of REACH**

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:

Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route, specified as follows:

- **Ten weeks pre-mating 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 shall be followed to weaning; and**
- **Cohort 3 (Developmental immunotoxicity).**

You must report the study performed according to the above specifications. Any expansion of the study 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 X of REACH, if you have

registered a substance at above 1000 tpa.

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

The Appendix states the reasons for the request for information to fulfil the requirements set out in the respective Annexes of REACH.

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. The timeline has been set to allow for sequential testing where relevant.

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>.

Approved¹ 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 requests to comply with Annex X of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier at a tonnage above 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to REACH.

Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

The basic test design of an Extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is a standard information requirement under Annex X to REACH. Furthermore Column 2 of Section 8.7.3. defines when the study design needs to be expanded.

You have provided

- (i) A "Preliminary Developmental Toxicity Screen" study (1997, guideline EPA OTS 798.4420), and
- (ii) A reference to an earlier decision requesting an EOGRT study on the Substance.

We have assessed this information and identified the following issue(s):

- A. With reference to (i), although you do not explicitly claim an adaptation, ECHA understands that the "Preliminary Developmental Toxicity Screen" study was submitted in order to meet the required information by way of adaptation under Annex XI, Section 1.1.2. This adaptation rule enables registrants to claim that the data from experiments not carried out according to GLP or the test methods referred to in Article 13(3) can be considered equivalent to data generated by those test methods.

However, a number of cumulative conditions need to be met, including:

- Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3), in this case OECD TG 443 as specified in the request.

The study you provided does not meet this condition, because the exposure duration in the provided study was "Gestation days 6 through 15" for the female F0 animals. This is not comparable to the requirement of a continuous exposure from ten weeks before mating until the end of lactation for the parental (P0) generation, and continuous exposure of the F1 generation starting from *in utero* and continuing postnatally up to adulthood as well as during extension of Cohort 1B until termination of F2 generation.

Therefore, the information you provided does not fulfil the information requirement.

- B. In (ii), you have provided a reference to an earlier decision² requesting an EOGRT study on the Substance but no information that would fulfil the information requirement of Annex X, 8.7.3.

Therefore, based on the above issues A and B, an EOGRT study is required.

In your comments, you agree to perform the requested study.

The specifications for the study design

Premating exposure duration and dose-level setting

The length of pre-mating exposure period must be ten weeks to cover the full spermatogenesis

² <https://echa.europa.eu/documents/10162/769fdf7a-fa5d-e1d0-68eb-761c39c5181a>

and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks pre-mating exposure duration is required if there is no substance specific information in the dossier supporting shorter pre-mating exposure duration as advised in the ECHA Guidance³. In this specific case ten weeks exposure duration is supported by the lipophilicity of the Substance ($\log K_{ow} > 6$ at 20°C) to ensure that the steady state in parental animals has been reached before mating.

Therefore, the requested pre-mating exposure duration is ten weeks.

In order to be compliant and not to be rejected due to too low dose levels, the highest dose level shall 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. 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 relevant data to be used for dose level setting, it is recommended that range-finding results are reported with the main study.

You have to provide a justification with your study results that demonstrates 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.

Extension of Cohort 1B

If the Column 2 conditions of 8.7.3., Annex X are met, Cohort 1B must be extended.

The extension is inter alia required, if the use of the registered substance is leading to significant exposure of consumers and professionals (column 2, first paragraph, lit. (a) of Section 8.7.3., Annex X) and if there are indications that the internal dose for the registered substance will reach a steady state in the test animals only after an extended exposure (column 2, first paragraph, lit. (b), second indent of Section 8.7.3., Annex X).

The use of the Substance is leading to significant exposure of consumers and professionals because the Substance is used by professionals in floorings and adhesives (PROCs 4, 5, 10, 13) and by consumers in "DIY products" such as adhesives and sealants (e.g. glues for hobby use).

In addition, there are indications that the internal dose for the Substance will reach a steady state in the test animals only after an extended exposure. Specifically, the $\log K_{ow}$ for the substance is above 4.5 indicating potential accumulation. Section 7.1 of IUCLID (toxicokinetics) also acknowledges that "*once absorbed, the substance may potentially bind to circulatory proteins and accumulate in adipose tissues*".

Therefore, Cohort 1B must be extended.

³ ECHA Guidance R.7a, Section R.7.6.

The F2 generation shall 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 151⁴. It is recommended to aim to 20 litter per dose group in order to have similar statistical power for investigations than in P0 generation.

Cohort 3

The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity.

Existing information on the Substance itself derived from the available OECD TG 408 study (2018) shows evidence of immunotoxicity in all treated groups in males:

- Reduced lymphocyte counts (statistically significant)
- Dose-dependently reduced spleen weights (-7.3% in low dose; -9% in mid dose; and -16% in high dose with statistical significance).

Furthermore, the substance has a harmonised classification for Skin Sens 1.

Therefore, the developmental immunotoxicity Cohort 3 needs to be conducted.

Species and route selection

The study must be performed in rats with oral⁵ administration.

Further expansion of the study design

No triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) were identified. However, you may expand the study by including Cohorts 2A and 2B if relevant information becomes available from other studies or during the 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 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 Guidance³.

Deadline to submit the requested information in this decision

The timeline indicated in the draft decision to provide the information requested is 24 months from the date of adoption of the decision.

In your comments on the draft decision, you requested an extension of the timeline. You justified your request with previous experience on conducting EOGRT studies, and discussions at EUROTOX 2019 meeting.

As a response to ECHA's request, you provided documentary evidence from your selected test laboratory. Based on this estimated timeline, you anticipate to update your dossier approximately by the 24-month requirement.

Therefore, ECHA has not modified the deadline of the decision.

⁴[http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO\(2013\)10&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2013)10&doclanguage=en)

⁵ ECHA Guidance R.7a, Section R.7.6.2.3.2.

Appendix B: Procedural history

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.

On 30 March 2017 ECHA issued decision CCH-D-2114357257-44-01/F².

On 11 February 2019 the registrant updated the dossier and provided the results of the 90-day sub-chronic toxicity study.

On 12 April 2019 ECHA informed the registrants that the request for an EOGRT study was withdrawn and would be addressed in this separate decision.

The compliance check was initiated on 2 May 2019.

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

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

ECHA took into account your comments and did not amend the deadline.

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 C: Observations and technical guidance

1. The substance subject to the present decision is provisionally listed in the Community rolling action plan (CoRAP) for the start of substance evaluation in 2021.
2. This compliance check decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.
3. 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 the Member States.

4. 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 shall 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.

5. 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

⁶ <https://echa.europa.eu/practical-guides>

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”.

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.

6. List of references of the ECHA Guidance and other guidance/ reference documents⁸

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 in this decision.

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

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.

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>

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.

OECD Guidance documents¹⁰

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.

¹⁰ <http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm>

Appendix D: 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]
[REDACTED]	[REDACTED]	[REDACTED]
[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.