EUROPEAN CHEMICALS AGENCY

Helsinki, 21 August 2020

Addressees
Registrant of CH334-00086_SIKA Hardener AI listed in the last Appendix of this decision

Date of submission for the submitted dossier subject of a decision
16 October 2019

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: 3-[(3-{[(3-acetoxy-2,2-dimethylpropylidene)amino]methyl}-3,5,5-trimethylcyclohexyl)imino]-2,2-dimethylpropyl acetate
EC number: 805-722-7
CAS number: 1064082-81-0

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 ***30 August 2021***.

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

1. In vivo mammalian erythrocyte micronucleus test (Annex VIII, Section 8.4., column 2; test method: OECD TG 474) in mice or rats, oral route.

Conditions to comply with the requests

You are bound by the requests for information corresponding to the REACH Annexes applicable to your own registered tonnage of the Substance at the time of evaluation.

Therefore, you have to comply with the requirements of Annexes VII and VIII of REACH, if you have registered a substance at 10-100 tpa.

The Appendices state the reasons for the requests 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.

Appeal

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 requirements applicable to all the Registrants subject to Annex VIII of REACH

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

1. **In vivo mammalian erythrocyte micronucleus test (Annex VIII, Section 8.4., column 2)**

Under Annex VIII to REACH, an appropriate *in vivo* mutagenicity study shall be considered if there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII.

Your dossier contains positive results for the *in vitro* cytogenicity test which raises a concern for chromosomal aberration.

Therefore, the condition set out in Annex VIII, Section 8.4, column 2 is met and the information requirement for an appropriate *in vivo* mutagenicity study is triggered.

Your dossier contains no data from an *in vivo* mutagenicity study. You have submitted a testing proposal for an *in vivo* mammalian erythrocyte micronucleus assay ("MN test", OECD TG 474) to be performed with the Substance. You have provided following justification and specification for the study:

"*The test substance is proposed to be administered orally by gavage to mice. Doses will be based on data available for acute as well as repeated oral toxicity studies. Based on the results of the acute and repeated oral toxicity studies and taken the OECD requirements into consideration, a maximum dose of 2000 mg/kg bw/day, and two additional doses (separated by a factor of 2 to 4) are proposed at a single administration.*

It is further proposed to assess the erythrocytes of the bone marrow, rather than peripheral blood, since there is more experience and historical control data available for this approach which makes it more reliable.

Six animals per dose or control group are proposed to reach a minimum of five analysable animals for one sex according to the Guideline. Since the available data did not demonstrate relevant differences between males and females, the use of males only is proposed."

ECHA notes that even though your justification above refers to mice, the 'Test animals' section of your testing proposal defines rat as the species to be tested.

ECHA requested your considerations for alternative methods to fulfil the information requirement for Genetic toxicity in vivo. ECHA notes that 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.

a) Test selection

According to the ECHA Guidance Chapter R.7a[2], the proposed MN test is an appropriate test to investigate effects on chromosomal aberrations if the test substance or its metabolite(s) will reach the target tissue as specified in the respective test method (OECD TG 474).

[2] ECHA Guidance Chapter R.7a, Section R.7.7.6.3

b) Test design

Your testing proposal refers to mice and rats as the species to be tested. According to the test method OECD TG 474, the test must be performed in mice or rats.

You propose administration via oral (gavage) route. Having considered the anticipated routes of human exposure and adequate exposure of the target tissue(s), performance of the test by the oral route is appropriate.

You propose a single administration of a maximum dose of 2000 mg/kg bw/day, and two additional doses (separated by a factor of 2 to 4).

According to OECD TG 474 (para 36) "*Preferably, 2 or more treatments are performed, administered at 24-hour intervals [...] In the alternative, single treatments can be administered, if scientifically justified*". You did not provide any justification for a single administration. Furthermore, with a single administration scheme, samples of bone marrow are taken at least twice from independent groups of animals, whereas with two treatments, samples are collected only once, i.e. reducing the number of animals needed. Therefore, ECHA requires two treatments separated by 24-hours.

OECD TG 474 describes dose level setting in paragraphs 30-33. In setting the dose levels, you must take into consideration the Guideline requirements, the requirement for two treatments, and the available data.

You propose to assess the erythrocytes of bone marrow, rather than peripheral blood. According to OECD TG 474, you can choose between bone marrow and peripheral blood. Therefore, ECHA agrees with your proposal to assess erythrocytes of the bone marrow.

Furthermore, you state "*Since the available data did not demonstrate relevant differences between males and females, the use of males only is proposed*". ECHA agrees that the available repeat-dose (OECD TG 422) and acute (OECD TG 402) data did not show differences in systemic toxicity, and therefore testing in one sex is acceptable.

Regarding the exposure of the target tissue, the applicable test guideline (OECD TG 474) states "If there is evidence that the test substance(s), or its metabolite(s), will not reach the target tissue, it may not be appropriate to use this test". Additionally, a negative test result can be considered reliable if "Bone marrow exposure to the test substance(s) occurred". Accordingly, if the Substance is negative in this test, but it is not possible to demonstrate that bone marrow exposure to the Substance occurred, then ECHA will consider any remaining uncertainty concerning the mutagenic potential of the Substance and whether to request any further information.

c) Germ cells

You may consider to collect male gonadal cells (spermatogonia) at the same time as the other tissues, in order to limit additional animal testing. You can prepare the slides for male gonadal cells and store them for several months at room temperature, in dry conditions and protected from light. Following the generation and analysis of data on somatic cells, you should consider analysing the slides prepared with spermatogonia, using the mammalian spermatogonial chromosome aberration test (OECD TG 483). This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

d) Outcome

Under Article 40(3)(b) of REACH, you are requested to carry out the proposed test under modified conditions, as explained above, with the Substance: *In vivo* mammalian erythrocyte micronucleus test (test method: OECD TG 474) in mice or rats, oral route.

In your comments on the draft decision, you agree to conduct the requested test as specified in the decision.

Appendix B: Procedural history

ECHA received your registration containing the testing proposal for examination on 17 October 2019.

ECHA held a third party consultation for the testing proposals from 17 December 2019 until 31 January 2020. ECHA did not receive information from third parties.

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.

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

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. 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'[3].

4. Test material

   Selection of the test material(s)

   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 is known to have or could have 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.

   Technical reporting of the test material

   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.

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

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[4].

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

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)[6]

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.

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 Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

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

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]

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.