EUROPEAN CHEMICALS AGENCY

Helsinki, 9 June 2020

Addressees
Registrants of Sodium 4-oxovalerate listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of a decision
12/04/2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Sodium 4-oxovalerate
EC number: 243-378-4
CAS number: 19856-23-6

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 March 2022***.

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

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method OECD TG 408) in rats with Levulinic acid, EC No 204-649-2, CAS No 123-76-2 ('the analogue substance');

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method OECD TG 414) in a first species (rat or rabbit), oral route with the analogue substance.

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, VIII and IX of REACH, if you have registered a substance at 100-1000 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 on general considerations addresses common arguments that are applicable throughout the present decision while the Appendix A states the reasons for the requests for information to fulfil the requirements set out in the respective Annex of REACH.

The testing material used to perform the required studies shall be selected and reported in accordance with the specifications prescribed in Appendix C Observations and technical guidance.

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 on general considerations

The ECHA Guidance documents referred to in this decision are listed in Appendix C of this decision.

(i) Assessment of the Grouping of substances and read-across approach, in light of the requirements of Annex XI, Section 1.5.

The decision of ECHA is based on the examination of the testing proposals submitted by you for the Substance.

In relation to the testing proposals subject to the present decision, you propose a testing strategy intending to fulfil the standard information requirement for:

- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

In IUCLID, Sections 7.5.1 and 7.8.2, you propose to test the analogue substance (Levulinic acid, EC No 204-649-2, CAS No 123-76-2) for the above mentioned information requirements. You propose to use the results obtained to adapt the standard information requirements for the Substance by using a grouping and read-across approach according to Annex XI, Section 1.5. of the REACH Regulation.

ECHA has considered the scientific and regulatory validity of your proposed grouping and read-across approach in general before assessing the specific standard information requirements in the following appendix.

Grouping of substances and read-across approach
Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group.

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance[2] and related documents[3, 4].

You have provided a read-across justification document in IUCLID Section 13.

You have provided the following reasoning for the prediction of toxicological properties:
In your read across hypothesis you state that "*The Read-across (RA) approach discussed is based on the hypothesis that source and target substance have similar toxicological properties based on their structural similarity and the comparable physicochemical properties. Furthermore, this hypothesis is supported by the comparable metabolism and mechanistic profile between two substances. The target substance is the sodium salt of the*

[2] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of
Chemicals. 2008 (May) ECHA, Helsinki. 134. pp. Available online:
https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf/77f49f81-b76d-40ab-8513-4f3a533b6ac9

[3] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)

[4] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://doi.org/10.2823/794394

similar substance and it is therefore expected to dissociate to the same active moiety (levulinate anion) and have identical toxicological profile".

ECHA understands that you predict the properties of the Substance using a read-across hypothesis which is based on the formation of common (bio)transformation products. The properties of your Substance are predicted to be quantitatively equal to those of the analogue substance.

ECHA agrees that the structure of the analogue substance is similar to the Substance, because the Substance is a sodium salt of the analogue substance.

Moreover, concerning the prediction of toxicological properties, ECHA agrees that similarity in the metabolic profile and toxicological properties of the Substance and the analogue substance is likely. You indicated in the dossier and ECHA agrees that both substances will dissociate in water and result in common species in the acidic conditions of the stomach. Therefore, ECHA considers that the analogue substance can be used to predict the toxicological properties of the Substance.

As explained above, you have established that relevant properties of the Substance can be predicted from data on the analogue substance. ECHA agrees with your read-across hypothesis. However, we emphasise that any final determination on the validity of your read-across adaptation will only be possible when the information on requested studies will be available in the dossier.

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.

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

A sub-chronic toxicity study (90 day) is a standard information requirement under Annex IX, Section 8.6.2. to REACH.

You have submitted a testing proposal for a sub-chronic toxicity study (90 day) by the oral route according to OECD TG 408 with the analogue substance.

You provided your considerations and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

ECHA has assessed the proposed read-across approach and agrees with the proposed hypothesis as explained under the Appendix on general considerations.

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

You did not specify the species to be used for testing. According to OECD TG 408, the rat is the preferred species.

According to Article 40(3)(a) of the REACH Regulation, you are requested to carry out the proposed test with the analogue substance.

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX, Section 8.7.2. to REACH.

You have submitted a testing proposal for a PNDT study according to OECD TG 414 with the analogue substance, in the rat, by the oral route.

You provided your considerations and you applied read-across to fulfil the respective information requirement, and no other alternative methods were available. ECHA has taken these considerations into account.

ECHA has assessed the proposed read-across approach and agrees with the proposed hypothesis as explained under the Appendix on general considerations.

Species

You proposed testing with the rat as a first species. You may select between the rat or the rabbit because both are preferred species under OECD TG 414.

Route

You proposed testing by the oral route. ECHA agrees with your proposal. The oral route is the most appropriate route of administration to investigate reproductive toxicity[5].

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

Under Article 40(3)(a) of REACH, you are requested to carry out the proposed test with the analogue substance.

Appendix B: Procedural history

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 12 April 2018.

ECHA held a third party consultation for the testing proposals from 18 June 2018 until 2 August 2018. 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 the REACH.

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 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 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 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]'

4. Test material

   Selection of an analogue substance test material

   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. When testing an analogue substance, the test material selected must be representative of the specified analogue substance. The selection of test material must support the read-across prediction, as presented in the read-across justification document.

   While selecting the test material you must take into account the impact of each constituent/ impurity on the test results for the endpoint(s) to be assessed. For example, if a constituent/impurity of the analogue substance is known to have an impact on (eco)toxicity, the selected test material must contain that constituent/impurity.

   Technical reporting of an analogue substance 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.

   Further instructions on what needs to be reported for the analogue substance test material composition are available in Practical Guide on "How to use alternatives to animal testing to fulfil your information requirements" (Chapter 4.4.).

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

5. List of references of the ECHA Guidance documents[7]

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)[8]

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.

[7] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[8] 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]
[redacted]	[redacted]	[redacted]