~~Confidential~~

Helsinki, 24 June 2021

Addressees
Registrants of barium sulfate ec 231-784-4 listed in the last Appendix of this decision

Date of submission of the dossier subject of a decision
03/02/2020

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Barium sulfate
EC number: 231-784-4
CAS number: 7727-43-7

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 ***3 January 2022***.

We note that the Substance has been registered as nanoforms by one of the registrants. This indicates that the Substance is manufactured or imported in the European Union in nanoforms. Annex VI of the REACH Regulation requires the submission of specific information for all nanoforms covered by the registration. Under Annex VI, the information must also be reported in the registration dossier in such a manner that it is clear which information in the joint submission pertains to each nanoform of the substance and which information pertains to the non-nanoform. However, in the current registration dossier it is not clear whether the testing proposal pertains to the nanoforms of the substance or to the non-nanoform. To the extent that the registrants propose to test an analogue substance that is not registered with nanoforms, the present decision evaluates whether the testing proposal is tailored to real information needs only in relation to the non-nanoform of the Substance.

Based on the above, the present decision requires a study to fulfil the information requirement only applicable to the non-nanoform of the Substance. Therefore, this decision is without prejudice to any future regulatory action against the possible incompleteness or incompliance of the information in the dossier pertaining to the nanoforms of the Substance.

A. 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

   with the analogue substance barium$^{(2+)}$ dichloride dihydrate (EC number 600-412-6).

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 appendix:

- Appendix entitled "Reasons to request information required under Annex X of REACH".

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 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.

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". 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 X of REACH

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

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 (Section 8.7.3.) to the REACH Regulation. Furthermore, column 2 of Section 8.7.3. defines when the study design needs to be expanded.

You have submitted a testing proposal for an EOGRTS according to OECD TG 443 by the oral route in rats with 10 week premating exposure duration with the analogue Substance barium$^{(2+)}$ dichloride dihydrate (EC number 600-412-6). You have provided the following justification and specification of the study design according to the criteria described in Column 2 of Section 8.7.3, Annex X:

"*The study will be performed in rats according to OECD guideline 443 in compliance with GLP. The test substance will be administered by the oral route. The basic configuration of the EOGRTS will be performed as based on the toxicological profile of the substance there are no concern-driven scientific triggers for the performance of the F2 generation (extension of Cohort 1B), developmental neurotoxicity (DNT; cohorts 2A and 2B) and/or developmental immunotoxicity (DIT; cohort 3) cohorts.*
1) Extension of Cohort 1B and termination time for F2: extension not justified […] The substance has no uses leading to significant exposure of consumers or professionals. The substance has only a limited professional use, which is not expected to affect many users. [..] The substance is not classified as Mutagen Category 1A or 1B or 2. […] The substance is not classified as a PBT or vPvB. The toxicokinetic behaviour of the substances gives no hints for very slow clearance, the NOAEC/LOAEC of subchronic studies are not more than 3 times lower than that the NOAEC/LOAEC from a subacute study. Therefore there are no indications that the internal dose for the substance will reach a steady state in the test animals only after an extended exposure. –[…] There are no indications based on the available study results that endocrine disruption is a relevant mode of action for the substance.
[…] 2) Inclusion of Cohorts 2A and 2B (developmental neurotoxicity, DNT) and/or Cohort 3 (developmental immunotoxicity): not justified The available data on barium chloride do not indicate a particular concern on neurotoxicity and/or immunotoxicity and therefore the inclusion of the developmental neurotoxicity (Cohorts 2A and 2B) and/or developmental immunotoxicity (Cohort 3) is not considered justified".

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.

Evaluation of read-across approach

You proposed to adapt this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5.

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 the reference substance(s) within the group (addressed under 'Assessment of prediction(s)').

You provided a hypothesis pointing out that *"the toxicity of barium substances such as barium sulfate can reasonably assumed to be determined by the availability of barium ions in solution. As a first surrogate for bioavailability, the water solubility of a test substance may be used. Barium chloride is highly water soluble with ca. 375 g/L at pH ca. 6.5, whereas barium sulfate is poorly soluble (3.1 mg/L at pH 9). Hence, any read across from barium chloride to barium sulfate is inherently very conservative"*.

ECHA agrees that the information provided supports your hypothesis and your hypothesis is accepted.

Therefore, you have established that relevant properties of the Substance can be predicted from data on the analogue substance. ECHA emphasises 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.

Study design

The proposed study design fulfils the information requirement.

The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

You proposed ten weeks premating exposure. ECHA agrees with your proposal.

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA Guidance R.7a.

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.

Species and route selection

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

Outcome

Under Article 40(3)(a) of REACH, you are requested to provide the proposed test with the analogue Substance barium$^{(2+)}$ dichloride dihydrate (EC number 600-412-6).

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 Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B 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 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[2].

Available data

The study requested in this decision has been performed since you proposed this test. In accordance with Title III of the REACH Regulation, you must obtain access to that data and make every effort to reach an agreement on the sharing of data and costs.

ECHA considers six months sufficient for you to seek permission from the study owner to refer to the other registrants' full study report.

[2] ECHA Guidance R.7a, Section R.7.6.

Appendix B: 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[3].

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:
   a) its representativeness towards the specified analogue substance,
   b) it supports the read-across prediction as as presented in the read-across justification document,
   c) the impact of each constituent/ impurity on the test results for the endpoint 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.

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.

With that detailed information, ECHA can confirm 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 Practical Guide on How to use alternatives to animal testing to fulfil your information requirements (Chapter 4.4.)[4].

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

Appendix C: Procedure

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 7 February 2020.

ECHA held a third party consultation for the testing proposal(s) from 17 June 2020 until 3 August 2020. ECHA did not receive information from third parties. ECHA did receive information from the registrant during the third party consultation. ECHA has addressed this aspect in the notification letter to the draft decision.

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 did not receive any comments within the commenting period.

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.

You did not provide any comments on the proposed amendment(s).

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 D: List of references - ECHA Guidance[5] 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)[6]

RAAF - considerations on multi-constituent substances and UVCBs (RAAF UVCB, March 2017)[6]

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.

[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

OECD Guidance documents[7]
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.

[7] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix E: 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]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[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.