EUROPEAN CHEMICALS AGENCY

Helsinki, 08 December 2020

Addressees
Registrant(s) of JS_strontium as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
30/05/2017

Registered substance subject to this decision ("the Substance")
Substance name: Strontium
EC number: 231-133-4
CAS number: 7440-24-6

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***15 March 2023***.

Requested information must be generated using the Substance unless otherwise specified.

A. Information required from all the Registrants subject to Annex IX of REACH

1. Extended one-generation reproductive toxicity study (triggered by Annex IX, Section 8.7.3., column 1; test method: OECD TG 443) by oral route, in rats, 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 shall be followed to weaning;
   - Cohorts 2A and 2B (Developmental neurotoxicity).

   You must report the study performed according to the above specifications. Any expansion of the study must be scientifically justified.

Reasons for the request(s) are explained in the following Appendix entitled "Reasons to request information required under Annexes IX 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, VIII and IX to REACH, for registration at 100-1000 tpa.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

For certain endpoints, ECHA requests the same study from registrants at different tonnages. In such cases, only the reasoning why the information is required at lower tonnages is provided in the corresponding Appendices. For the tonnage where the study is a standard information requirement, the full reasoning for the request including study design is given. Only one study is to be conducted; the registrants concerned must make every effort to reach an agreement as to who is to carry out the study on behalf of the other registrants under Article 53 of REACH.

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, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

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 IX of REACH

1. Extended one-generation reproductive toxicity study (Annex IX, 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 IX to REACH, 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 the conditions under which the study design needs to be expanded.

You have provided a read-across adaptation using reproductive toxicity study with the analogue substance strontium ranelate (CAS no 5459-90-4; [redacted], 2001). The study was performed according to the ICH Harmonised Tripartite Guideline - Detection of toxicity to reproduction for medical products, Washington June 24, 1993; ICH Harmonized Tripartite Guideline, Addendum: Toxicity to male fertility, July 1996.

In your comments to the draft decision, you disagree on the triggers for performing the test at Annex IX. You question whether the effects recorded in the Kroes et al. (1977) study meet the criteria of Column 1, Annex IX, section 8.7.3.

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

Adverse effects on reproductive organs or tissues or other concerns in relation with reproductive toxicity are observed in available studies. More specifically, there are indications of one or more modes of action related to endocrine disruption because in the sub-chronic study performed with the analogue substance strontium chloride (EC no 233-971-6), following a protocol similar or equivalent to OECD TG 408 (Kroes et al., 1977), the relative thyroid weights were statistically significant increased in males at 1200 ppm (corresponding approximately to 50 mg/kg bw/day) and 1400 ppm (by 33% ($p>0.01$) and 26% ($p>0.001$), respectively). There were no treatment-related changes in body weights in the study.

In the same study, the relative prostate weights were statistically significant decreased in males at 75 and 1200 ppm (by 28% ($p>0.01$) and 21% ($p>0.05$), respectively), and the relative pituitary weights were statistically significant decreased in females at 75 and 1200 ppm (by 16% ($p>0.05$) and 24% ($p>0.01$), respectively). Although there was no clear dose-response for the decrease in relative prostate and pituitary weights, the findings support triggering of the Extended one-generation reproductive toxicity study at Annex IX.

ECHA considers that the criteria in Column 1, Annex IX, section 8.7.3 are met because existing information shows evidence of deviations in hormonally sensitive organs in both sexes without notable general toxicity (see further ECHA Guidance R.7a, Appendix R.7.6–2 EOGRTS Study Design).

Regarding the mean relative prostate weight, you argue that the response was not dose related and there were no corresponding histopathological findings. You indicate that the finding might, for example, be due to methodological issues, and it could not be assumed that the effects on prostate weight (and not on other male reproductive organs) would result in effects on male fertility. ECHA agrees that histopathological findings are important and indeed sensitive markers. However, you have provided suggestions but not provided conclusive argument excluding a concern or the reliability of the study; an indication in prostate weight can be considered as supportive information among other of changes seen in hormonally sensitive organs.

You also note that historical control values were not reported in the study. ECHA agrees that historical controls would have been valuable, but considers that data from in-study control animals should be used, and that the absence of appropriate historical control values does not invalidate the study.

You further argue that an effect of strontium on the endocrine mediated mechanisms of toxicity or changes of hormone levels of the hypothalamic-pituitary-gonadal axis (HPG axis) is not applicable, based on the available data, because the effects on pituitary weights were observed only in females (in an absence of a dose - relation) and not in male animals. In females, no effect on reproductive organs (ovaries and uterus) were described. Thus, adverse effects on fertility or reproduction induced by strontium are not anticipated in consideration of the data provided. However, you have provided suggestions but not provided conclusive argument excluding a concern; ECHA considers that the decreasing trend in pituitary weights in treated females still indicate one or more modes of action related to endocrine disruption and therefore supports triggering together with other changes seen in hormonally sensitive organs.

For a response to your comments to the draft decision related to changes in thyroid weights please see further under "Cohorts 2A and 2B" below.

Based on the above ECHA retains the view that an EOGRT study according to OECD TG 443 as specified in this decision is an information requirement for your registration, because Column 1 criteria at Annex IX, section 8.7.3 are met.

According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across should:

[1] have adequate and reliable coverage of the key parameters addressed in the corresponding test methods referred to in Article 13(3), in this case an extended one generation reproductive toxicity study (OECD TG 443) which includes the following key parameters:
   a. full histopathology of organs and tissues (P0 and F1)

[2] cover an exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3), in this case (OECD TG 443) which includes, at least exposure of 10 weeks prior to pairing for P0 animals unless the Cohort 1B animals are mated to produce the F2 generation, which is followed to weaning.

In the provided study:

- For reproductive organs only weights were recorded and histopathology was only investigated from F0 males for epididymis and testes.
- F0 males were exposed for 28 days prior to pairing until six days after the treated females started littering. Females were exposed from day six of gestation until day twenty of lactation. The exposure in your study is considerably shorter than as required by OECD TG 443.

In your comments to the draft decision, you submitted a read-across justification. As the read-across approach under Annex XI, Section 1.5 in the draft decision was rejected based on adequacy and reliability of source studies, only and there is no information in the draft decision on other aspects of the submitted read-across justification, this information is therefore considered not relevant.

Therefore, the provided study, which specifically investigates male fertility, does neither investigate female fertility nor post-natal developmental toxicity until adhulthood.

Therefore, your adaptation is rejected and the information requirement is not fulfilled.

The specifications for the study design

Premating exposure duration and dose-level setting

The length of premating exposure period must be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

A 2-week premating exposure duration for P0 animals is sufficient for your Substance, because the F1 animals of Cohort 1B are mated to produce the F2 generation and, thus, the premating exposure duration will be 10 weeks for these Cohort 1B animals.

Therefore, the requested premating exposure duration is at least two 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 must be included.

Extension of Cohort 1B

If the Column 2 conditions of 8.7.3., Annex IX 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 IX) and

- there are indications of one or more relevant modes of action related to endocrine disruption from available *in vivo* studies or non-animal approaches (column 2, first paragraph, lit. (b), third indent of Section 8.7.3., Annex IX).

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 for (e.g. [redacted], and by consumers ([redacted]) for [redacted] (e.g. [redacted] with [redacted] and [redacted]).

Furthermore, there are indications of one or more modes of action related to endocrine disruption based on the organ weights of hormonally sensitive organs (thyroid, prostate and pituitary)as described above in the sub-chronic study performed with the analogue substance strontium chloride (EC no 233-971-6), following a protocol similar or equivalent to OECD TG 408 (Kroes et al., 1977).

Therefore, Cohort 1B must be extended.

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 151[2]. 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.

Existing information on the analogue substance strontium chloride (EC no 233-971-6) derived from a sub-chronic study following a protocol similar or equivalent to OECD TG 408 (Kroes et al., 1977), show evidence of thyroid toxicity in males. Relative thyroid weights were statistically significant increased at 1200 and 1400 ppm (by 33% ($p>0.01$) and 26% ($p>0.001$), respectively). There were no treatment-related changes in body weights in the study. Thyroid toxicity rises a particular concern on developmental neurotoxicity (ECHA Guidance R.7a).

In your comments to the draft decision, you state that the findings on thyroid weights by Kroes et al. (1977) showed a statistically significant (but not dose-related) increase, but that the increase in thyroid activity was not statistically significance between the high dose and the control group. Furthermore, no effects on the thyroid weight and the thyroid histopathology were seen in the female animals.

Based on the data presented in the study you conclude that direct effects on the thyroid and disruption of the thyroid modality are not anticipated, as an increased hormone production is not evidenced, since the authors reported explicitly that there was no parafollicular cell hyperplasia, and there were no corresponding effects on relative pituitary weights in males of the dose groups of 1200 and 4800 ppm where effects on thyroids were observed. Furthermore, pituitary weights were slightly decreased in females (300 and 4800 ppm) and low dosed males (75 ppm), and the histopathological examination of the pituitary showed no signs of activation or any other alteration. Thus, an activation of the HPT axis was not evidenced. Effects may thus be secondary, and possibly related to interactions between strontium and calcium.

You conclude that, based on the missing dose-response relationship and the missing significance of the histopathological finding, an adversity towards thyroids/thyroid signalling due to strontium exposure can be excluded.

ECHA notes that according to ECHA Guidance R.7a, Appendix R.7.6–2 EOGRTS Study Design, the statistically significant higher mean relative thyroid weights in males are an acceptable trigger from a repeated dose toxicity study. Furthermore, treated females may not have been unaffected as there was also a trend in increased mean relative thyroid weights also in treated females compared to controls.

ECHA concludes that available data indicate that, in the absence of overt general toxicity, the study by Kroes 1977 demonstrates a concern for thyroid toxicity. A concern for reproductive (and developmental) toxicity has therefore been identified and a need for further information

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

is triggered. Taken together, ECHA maintains its opinion that the mentioned effects are indicative of mode(s) of action related to endocrine disruption.

Therefore, the developmental neurotoxicity Cohorts 2A and 2B need to be conducted.

The study must be performed in rats with oral[3] administration.

ECHA notes that in your comment to the draft decision, you regard testing of your Substance as challenging due to its corrosivity. For that reason every effort must be taken to ensure administration of the test material in a form that minimises corrosion. Further information about testing of corrosive substances can be found in ECHA Guidance R. 7a, Section R.7.6.2.3.2. The dose selection used for the study should be justified.

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 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 IX. 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[4].

[3] ECHA Guidance R.7a, Section R.7.6.2.3.2.
[4] 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[5].

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:
   - the variation in compositions reported by all members of the joint submission,
   - the boundary composition(s) of the Substance,
   - 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.

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.

This information is needed to assess 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 manual on How to prepare registration and PPORD dossiers[6].

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

Appendix C: Procedure

This decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present. This decision does not prevent ECHA from initiating further compliance checks.

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 5 June 2019

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

ECHA took into account your comments and did not amend the request(s) or the deadline.

Extension of deadline
In your comments to the draft decision, you point out that registrants of several Joint Submissions have received draft decisions from ECHA with requests for studies on strontium and its salts. To be able to A) comply with Article 25 (1) and develop and justify a read-across approach, B) discuss with the CRO responsible to develop the study, and C) coordinate the activities of registrants of several Joint Submissions, you request an extension of the deadline for this decision from 24 to 30 months. ECHA disagrees with your request because regarding A) It is in your discretion to generate and provide the necessary supporting information in order to justify your read-across adaptation. If you do so, you are responsible for demonstrating the fulfilment of the requirements of Section 1.5 of Annex XI to REACH. If it fails and the resulting data does not support, or even contradict, your read-across hypothesis, you remain responsible for complying with this decision by the set deadline and regarding B) and C) the discussions with a contract organisation and the coordination of activities of registrants of several Joint Submissions are your responsibility. In any case, ECHA considers the deadline of 24 months sufficiently covers these activities in order to fulfil the standard information requirements. Therefore, ECHA did not extend the deadline of the draft decision.

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: List of references - ECHA Guidance[7] 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)[8]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, 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.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[9]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

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

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.

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]

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.