EUROPEAN CHEMICALS AGENCY

Helsinki, 11 September 2020

Addressees
Registrant of JS_Sodium Chlorate who has an opt-out listed in the last Appendix of this decision

Date of submission for the opt out dossier subject of this decision
22/06/2017

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Sodium chlorate
EC number: 231-887-4
CAS number: 7775-09-9

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

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***18 March 2021***.

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

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method OECD TG 414) in a second species (rat), oral route with the Substance.

2. 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:
   - 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 and
   - 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.

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 to X of REACH, if you have registered a substance at above 1000 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. 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.

Authorised[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.

EUROPEAN CHEMICALS AGENCY

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 abve 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X to REACH.

1. Pre-natal developmental toxicity study (Annex X, Section 8.7.2.) in a second species

Pre-natal developmental toxicity (PNDT) studies (OECD TG 414) in two species is a standard information requirement under Annex X to REACH.

Data in your dossier

You have provided a PNDT study in a first species (rabbit; [redacted] 2002) and the following justification for an adaptation of the PNDT study in a second species: "*The study does not need to be conducted on second species based on the outcome of the first test and all other relevant available data on toxicity to reproduction. See "cross reference" below.*"

ECHA understands that you refer to an adaptation of Annex IX, Section 8.7.2., Column 2, "*A decision on the need to perform a study at this tonnage level or the next on a second species should be based on the outcome of the first test and all other relevant available data.*"

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

In order to be compliant and enable concluding if the Substance is a developmental toxicant, information provided has to meet the requirements of OECD TG 414 in two species.

A pre-natal developmental toxicity study in a second species is a standard information requirement at Annex X unless one or more of the adaptations in Section 8.7 of Annex X or Annex XI apply, taking into account the results of the test in the first species or any other relevant avalable information.

You have not demonstrated that the results of a test in the first species or any other relevant available information enable adaptations in accordance with Section 8.7 of Annex X or Annex XI.

Weight of evidence adaptation in your comments on the draft decision

In your comments on the initial draft decision you "*propose to adapt the required standard information on the PNDT study in a second species according to the rules laid down in Annex XI (1.2) since there is sufficient weight of evidence from several independent sources of information loading to the conclusion that the substance does not cause developmental toxicity*".

In support of your adaptation, you refer to the following data:

(i) No adverse effects observed in a PNDT study according to OECD TG 414 with the Substance in rabbits.

(ii) No evidence of reproductive toxicity in a two-generation study (corresponding to the EPA Guideline OPPTS 870.3800 (Reproduction and Fertility Effects) conducted with an analogue substance (sodium chlorite).

Based on the presented sources of information, you argue that the available data gives sufficient information to conlude on the 2nd species pre-natal developmental toxicity because: *"there is sufficient weight of evidence from several independent sources of information loading to the conclusion that the substance does not cause developmental toxicity".*

Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

Annex XI, Section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

You have provided a justification for the weight of evidence adaptation as follows: *"There was no evidence of reproductive toxicity. Based on this information, it can be concluded that the substance does not cause developmental toxicity. Information on both rabbit (PNDT study) and rats (two-generation reproductive toxicity study) is available and a new PNDT study on rats would not provide new information. Moreover, there is no data to conclude that rats are more sensitive than rabbits in terms of developmental toxicity".* However, your justification does not include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study. In more detail, your justification does not explain why and how "no evidence on reproductive toxicity" can be translated to a conclusion that there is no prenatal developmental toxicity in two species (rat and rabbits), or that there is no species differences in pre-natal developmental toxicity for your Substance. Furthermore, in terms of species sensitivity, it is irrelevant that there is no data to conclude that rats are more sensitive than rabbits in order to adapt a study in rats. You have, however, not claimed, even less provided evidence, that rabbit is more sensitive than rats.

Irrespective of the above mentioned deficiencies on the documentation, which in itself could lead to the rejection of the adaptation, ECHA has assessed the provided sources of information.

Relevant information that can be used to support a weight of evidence adaptation for the information requirement of Section 8.7.2 at Annex X includes similar information that is produced by the OECD TG 414 on two species. The following key investigations are to be covered: 1) pre-natal developmental toxicity, 2) maternal toxicity, and 3) maintenance of pregnancy.

Pre-natal developmental toxicity, maternal toxicity and maintenance of pregnancy

Pre-natal developmental toxicity includes information on embryonic/foetal survival (numbers of live foetuses; number of resorptions and dead foetuses, postimplantation loss), growth (body weights and sixe) and structural malformations and variations (external, visceral and skeletal) after exposure *in utero*.

Maternal toxicity includes information after gestational exposure on maternal survival, body weights and clinical signs.

Maintenance of pregnancy includes information on abortions on early delivery as a consequence of gestational exposure.

The source of information (i) provides relevant information on pre-natal developmental toxicity, maternal toxicity and maintenance of pregnancy in rabbits exposed to the Substance. It does not provide any information on a second species.

The source of information (ii) provides relevant information on developmental toxicity, maternal toxicity and maintenance of pregnancy in rats exposed to an analogue substance (sodium chlorite). The source (ii) of information does not inform on structural malformations and variations (external, visceral and skeletal) as required in OECD TG 414.

Therefore, key investigations on pre-natal developmental toxicity (structural malformation and variations) in the rat are missing and, thus, not available in two species as required.

In addition, the reliability of these sources of information is significantly affected by the following deficiencies:

Section A.2. of the present Appendix identifies deficiencies of the read across approach used in your dossier. The same applies to your read-across for this weight of the evidence. As the read-across is rejected for the source of information (ii), it is not reliable and cannot be used under weight of evidence adaptation.

Due to missing relevant and reliable information on key investigations of pre-natal developmental toxicity in two species, and reliable information on maternal toxicity and maintenance of pregnancy in two species, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not a particular dangerous property.

Conclusion

Taken together, the relevant and reliable source of information as indicated above, provides some information on pre-natal developmental toxicity, but does not cover key information on structural malformations and variations (external, visceral and skeletal), maternal toxicity and maintenance of pregnancy in two species as required by the information requirement.

Therefore, a significant amount of essential investigations are limited or totally lacking that would inform on pre-natal developmental toxicity in two species in order to conclude on these aspects.

Your adaptations are rejected and the information requirement is not fulfilled.

The test in the first species was carried out by using a non-rodent species (rabbit). A PNDT study according to the test method OECD TG 414 must be performed in rat as preferred rodent species.

The study shall be performed with oral[2] administration of the Substance.

The jointly submitted registration for the Substance contains data which is relevant for this endpoint. In accordance with Title III of the REACH Regulation, you must request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs.

In your comments on the initial draft decision you explained that such a request places you in a situation of legal insecurity and dependent on other registrants.

Under Article 11(3) of REACH, a registrant has the right to opt out from a joint registration. ECHA has assessed the adaptation provided in your dossier and in your comments for this opted out information requirement, but as explained above it is rejected because the information included in the dossier does not comply with REACH.

In this case, a valid study on the Substance is already available in the joint submission. You are asked to request for it from the other registrants because, under REACH, unnecessary redundant animal testing must be avoided (Article 25).
Regarding your comments on becoming dependent on other registrants, Title III also provides for rights and obligations of the registrants for sharing these studies.

ECHA considers six months a sufficiently reasonable time for the registrant to seek permission to refer to the other registrant's full study report.

2. 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 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 adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5.

You have not provided a read-across justification document in IUCLID or in the CSR.

You predict the properties of the Substance from the structurally similar substance sodium chlorite, EC No. 231-836-6 (CAS No. 7758-19-2; i.e. the source substance).

The source study that you have used in your read-across approach, two-generation reproductive toxicity study, publication Gill et al. 2000 corresponds to the EPA Guideline OPPTS 870.3800 (Reproduction and Fertility Effects).

You have provided the following reasoning for the prediction of toxicological properties: "*The analogue substance sodium chlorite which shares the same functional group with the substance sodium chlorate also has comparable values for the relevant molecular properties.*"

ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The

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

properties of your Substance are predicted to be quantitatively equal to those of the source substance.

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 R.6 and related documents.

ECHA notes the following shortcoming with regards to the prediction of toxicological properties.

Observed differences in toxicological properties

Annex XI, Section 1.5. provides that "substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances. The observation of differences in the toxicological properties between the source substance(s) and the Substance is a warning sign. An explanation for such a difference resulting in a contradiction between the similarities in properties claimed in the read-across hypothesis and the observation of different properties needs to be provided and supported by scientific evidence.
As indicated above, your read-across hypothesis is based on the assumption that the structurally similar target and source substances cause the same type of effect(s).

The results of the information on repeated dose toxicity obtained with the target substance and the source substance vary. Specifically, the investigations of the two-generation reproductive toxicity study you provided with the source substance demonstrated haematological effects but no changes in thyroid hormone levels, whereas the repeated dose toxicity studies performed with the Substance show effects on thryoid (see below).

Furthermore, the source substance is acutely far more toxic (LD_{50} rat oral: 158 and 177 mg/kg bw/d for males and females, respectively) compared to the target substance (LD_{50} rat oral: 5000 mg/kg bw/d).

The available set of data on the target and source substances indicates differences in the toxicological properties of the substances. This contradicts your read-across hypothesis whereby the structurally similar target and source substances cause the same type of effect(s). Therefore you have not demonstrated and justified that the properties of the source substance(s) and of the Substance are likely to be similar despite the observation of these differences.

Based on the above, the information you provided does not fulfil the information requirement.

In your comments on the initial draft decision you explain that "*We will proceed with the update of the dossier in order to justify the read-across approach according to the current guidelines. ECHA should consider such an update prior to requesting additional studies since, according to the REACH Regulation, new tests on vertebrates shall only be conducted or proposed as a last resort when all other data sources have been exhausted (REACH Art. 25)*".

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 data does not support, or even contradict, your justification, you remain responsible for complying with this decision by the set deadline.

The following refers to the specifications of this required study.

Premating exposure duration and dose-level setting

Ten weeks premating exposure duration is required to obtain results adequate for classification and labelling and /or risk assessment. There is no substance specific information in the dossier supporting shorter premating exposure duration.[3]

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.

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 Substance itself derived from the available 90-day study shows evidence of effects on the thyroid at dose levels showing no remarkable other systemic toxicity:

- Thyroid colloid depletion in a 90-day study in rats at 128 mg/kg bw/d (moderate to marked severity, observed in all animals) (McCauley et al. 1995)
- Thyroid gland follicular hypertrophy in a 3-week study in rats at 500 mg/kg bw/d and above and in a 2-year study in rats at 35 mg/kg bw/d and above ([redacted] 2005)
- Significantly decreased T3 and T4 levels and increased TSH levels in male/female rats after 4 or 21 days of oral exposure in drinking water at 1 g/L or higher (Hooth *et al*. 2001)

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

Species and route selection

The study must be performed in rats with oral[4] administration.

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

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

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 Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B and 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 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[5].

Available data

The jointly submitted registration for the Substance contains data which is relevant for this endpoint. In accordance with Title III of the REACH Regulation, you must request it from the other registrant(s) and then make every effort to reach an agreement on the sharing of data and costs.

In your comments on the initial draft decision you explained that such a request places you in a situation of legal insecurity.

Under Article 11(3) of REACH, a registrant has the right to opt out from a joint registration. ECHA has assessed the adaptation provided in your dossier and in your comments for this opted out information requirement, but as explained above it is rejected because the information included in the dossier does not comply with REACH.

In this case, a valid study on the Substance is already available in the joint submission. You are asked to request it from the other registrants because, under REACH, unnecessary redundant animal testing must be avoided. Title III also provides for rights and obligations of the registrants for sharing these studies.

ECHA considers six months a sufficiently reasonable time for the registrant to seek permission to refer to the other registrant's full study report.

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

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.

The compliance check was initiated on 10 April 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 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 compliance check decision does not prevent ECHA from initiating further 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 the Member States.

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 the 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. 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.

   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.

   Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[7].

5. List of references of the ECHA Guidance and other guidance/ reference documents[8]

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

[7] https://echa.europa.eu/manuals

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

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.

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[10]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.
Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No 43, referred to as OECD GD43.

[9] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[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 fufilled
[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.