EUROPEAN CHEMICALS AGENCY

Helsinki, 01 April 2020

Addressees
Registrants of JS_sodium chlorite listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
08/02/2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Sodium chlorite
EC number: 231-836-6
CAS number: 7758-19-2

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

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 ***7 January 2022***.

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

1. The in vivo genotoxicity study also requested at B.1 (triggered by Annex VII, Section 8.4., column 2)

2. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method EU C.3./OECD TG 201) with the Substance;

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

1. In vivo mammalian alkaline comet assay (Annex IX, Section 8.4., column 2; test method OECD TG 489) in rats, oral route, on the following tissues: liver, oral: glandular stomach and duodenum with the Substance;

C. 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

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 Annex VII of REACH, if you have registered a substance at 1-10 tonnes per annum (tpa), or as a transported isolated

intermediate in quantity above 1000 tpa;

- 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;
- you have to comply with the requirements of Annexes VII to X of REACH, if you have registered a substance at above 1000 tpa.

Registrants are only required to share the costs of information that they must submit to fulfil the information requirements for their registration.

The same information is required from registrants at several appendices of this decision. The reasons for triggering of the requested information are provided in the corresponding appendices while the selection and design of the requested studies is examined in Appendices A and C. When the same study is required in this decision under several annexes of REACH, the registrants concerned shall make every effort to reach an agreement as to who is to carry out the study on behalf of the other registrants in accordance with Article 53 of REACH.

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.

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 for the requests to comply with Annex VII of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier registered at 1 to 10 tonnes or more per year must contain, as a minimum, the information specified in Annex VII to REACH.

1. The in vivo genotoxicity study also requested under B.1 (triggered by Annex VII, Section 8.4., column 2)

Under Annex VII to REACH, further mutagenicity studies must be considered in case of a positive result in an *in vitro* gene mutation study in bacteria.

You have provided the following studies in your dossier:

For the gene mutation endpoint:

i. Two *in vitro* studies (weight of evidence, similar to OECD guideline 471 (Bacterial Reverse Mutation Test): Fujita (1987) negative and Ishidate (1984) with sodium chlorite positive in *S. typhimurium* strain TA 100 with metabolic activation.
ii. One *in vitro* key study ([redacted] 1986), equivalent or similar to OECD Guideline 476 (In Vitro Mammalian Cell Gene Mutation Test) with chlorine dioxide (EC 233-162-8) with positive results in the presence and absence of metabolic activation.

For the cytogencity endpoint:

i. One *in vitro* study similar to OECD Guideline 473 (In Vitro Mammalian Chromosome Aberration Test) (Ishidate M (1984), positive.
ii. Eight *in vivo* cytogencity studies (weight of evidence): Meyer et al.1985 (Micronucleus assay 04) – negative, Meyer et al.1985 (Chromosome aberration assay – one single dose 05) – negative, Meyer et al. 1985 (Chromosome aberation assay-5 days), Meyer et al.1985 (Sperm head anomalies – 07) – negative, Hayashi et al.1988 (Micronucleus assay -02)- negative, Hayashi et al.1988 (Micronucleus assay -01) - intraperitoneal- positive, Hayashi et al.1988 (Micronucleus assay -03) - oral gavage – negative, Wang et al. 2002 (Micronucleus assay – 08) - negative).

We have assessed this information and identified the following issue:

A positive result in an *in vitro* gene mutation study in bacteria raises a specific concern for gene mutation that must be addressed including, where relevant, further studies appropriate for that specific concern.

Your dossier contains a positive result for the *in vitro* gene mutation study in bacteria, which raises the concern for gene mutation. It also contains positive results for an *in vitro* chromosomal aberration study and an *in vitro* gene mutation in mammalian cells study. You also provided several *in vivo* studies that address cytogenicity.

However, the concern for gene mutation raised by the positive *in vitro* gene mutation study in bacteria has not been followed up by an appropriate *in vivo* mutagenicity study. The *in vivo* studies submitted in your dossier do not address the gene mutation concern. In addition they are inadequate studies for the reasons described under Section B.1.

ECHA considers that an appropriate *in vivo* follow up mutagenicity study is necessary to address the concern identified *in vitro*.

According to the ECHA Guidance Chapter R.7a[2], the comet Assay is suitable to follow up the

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

positive *in vitro* result for gene mutation and chromosomal aberrations. Therefore, this test is the most appropriate for the Substance.

The selection of the appropriate test (comet assay) and its design are explained under Section B.1.

2. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

Growth inhibition study aquatic plants is a standard information requirement in Annex VII to REACH.

You have provided a key study and one supporting study in your dossier.

i. An EPA OPP 122-2 study / [redacted] (1991)
ii. A non-guideline study / Van Wijk et al. (1998)

We have analysed this information and have identified the following issue.

Tests on substances must be conducted in accordance with the OECD test guidelines or another recognised international test method (Article 13(3) of REACH). OECD TG 201 is the preferred guideline to fulfil this information requirement. OECD TG 201 in combination with the revised OECD Guidance 23, ENV/JM/MONO(2000)6/REV1 require(s) that the following conditions are met (among others):

- analytical monitoring of exposure concentrations.
- effect concentrations based on the measured values rather than nominal values unless the test concentrations are maintained within the required 20% of the measured initial concentrations throughout testing.
- For difficult to test substances, including rapidly transformed substances, a sufficiently sensitive analytical method is particularly necessary due to the likelihood of losses of the Substance from the test medium. The possibility of losses during sampling, sample treatment and analysis must be considered and documented.

In the supporting study by Van Wijk et al. (1998) there is no analytical monitoring. In the key study by [redacted] (1991) the you state that although you validated the analytical method in deionised water you were unable to validate the analytical method in the test medium.

Additionally, you have based the effect values on nominal concentrations but you did not demonstrate that the test substance concentration during the tests was maintained within 20% of the measured initial concentrations.

In your comments on the draft decision you explain that "*the test substance could not be monitored in the test solutions due to background interference* [from] *the chlorite and nitrite present in the natural groundwater used as dilution water*". However, you specify that in a chronic laboratory study on *Daphnia magna* ([redacted] 2008) conducted under flow-through conditions exposure concentrations were maintained within 20% of the nominal concentrations. You consider that the results of this chronic study are supportive that the exposure was stable in the studies by [redacted] 1991 (key studies) as according flow-through systems and higher test concentrations were used.

We first note that the full study report on the [redacted] (1991) study attached to your technical dossier specifies that the test was conducted under static conditions. Similarly the supporting study by Van Wijk et al. (1998) was also conducted under static conditions. Hence the results of the analytical monitoring conducted in the long-term invertebrates toxicity study

under flow-though conditions cannot be regarded as a valid justification that exposure was stable the growth inhibition studies on aquatic plants conducted under static conditions.

Therefore, the aforementioned conditions of the guidelines are not met, therefore the information provided does not fulfil the information requirement.

Appendix B: Reasons for the requests to comply with Annex IX of REACH

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII-IX to the REACH Regulation.

1. In vivo mammalian alkaline comet assay (Annex IX, Section 8.4., column 2)

Under Annex IX to REACH, the information requirement for an appropriate *in vivo* somatic cell genotoxicity study is triggered if there is a positive result in any of the in vitro genotoxicity studies in Annex VII or VIII and there are no appropriate results already available from an *in vivo* somatic cell genotoxicity study.

You have provided the following studies in your dossier:

i. For the gene mutation endpoint:Two *in vitro* studies (weight of evidence, similar to OECD guideline 471 (Bacterial Reverse Mutation Test): Fujita (1987) negative and Ishidate (1984) with sodium chlorite positive in *S. typhimurium* strain TA 100 with metabolic activation.
ii. One *in vitro* key study ([redacted] 1986), equivalent or similar to OECD Guideline 476 (In Vitro Mammalian Cell Gene Mutation Test) with chlorine dioxide (EC 233-162-8) with positive results in the presence and absence of metabolic activation.

For the cytogencity endpoint:
i. One *in vitro* study similar to OECD Guideline 473 (*In Vitro* Mammalian Chromosome Aberration Test) (Ishidate M (1984), positive.
ii. Eight *in vivo* cytogencity studies (weight of evidence): Meyer et al.1985 (Micronucleus assay 04) – negative, Meyer et al.1985 (Chromosome aberration assay – one single dose 05) – negative, Meyer et al. 1985 (Chromosome aberation assay-5 days), Meyer et al.1985 (Sperm head anomalies – 07) – negative, Hayashi et al.1988 (Micronucleus assay -02)- negative, Hayashi et al.1988 (Micronucleus assay -01) - intraperitoneal- positive, Hayashi et al.1988 (Micronucleus assay -03) -oral gavage – negative, Wang et al. 2002 (Micronucleus assay – 08) - negative).

We have assessed this information and identified the following issue:

To be considered adequate, the *in vivo* cytogenicity provided studies have to meet the requirements of OECD TG 474 (Mammalian Erythrocyte Micronucleus Test) or OECD TG 475, and the key parameters of theses test guidelines include:
a) For OECD TG 475 the mitotic index must be determined as a measure of cytotoxicity in at least 1000 cells per animal for all treated animals (including positive controls), untreated or vehicle/solvent negative control animals.
b) For OECD TG 474 at least 4000 immature erythrocytes per animal must be scored for the incidence of micronucleated immature erythrocytes.
c) For OECD TG 475 at least 200 metaphases must be analysed for each animal for structural chromosomal aberrations including and excluding gaps.

You provided several cytogencity *in vivo* studies performed according to OECD TG 474 (Mammalian Erythrocyte Micronucleus Test) or OECD TG 475 (Mammalian Bone Marrow Chromosome Aberration Test) with the Substance in order to follow up the concern for chromosomal aberration raised by the *in vitro* results. However, the above mentioned key parameter(s) are not met, because of the following deficiences:

- In the OECD TG 474 only 1000 immature erythrocytes per animal were scored for the incidence of micronucleated immature erythrocytes.
- In the OECD TG 475 study only 50 metaphases were analysed for each animal for structural chromosomal aberrations.
- The mitotic index was determined on only 500 cells per animal.

Therefore, the tests provided to follow-up the chromosomal aberration concern are not adequate.

Therefore, the provided *in vivo* tests are not adequate.

In case there are positive results *in vitro* studies showing concern for both chromosomal aberration and gene mutation, the ECHA Guidance Chapter R.7a[3], identifies the following tests as options for a follow-up *in vivo* study. The mammalian erythrocyte micronucleus test ("MN test", OECD TG 474), the mammalian bone marrow chromosomal aberration test ("CA test", OECD TG 475) or the *in vivo* mammalian alkaline comet assay ("comet Assay", OECD TG 489) are suitable to follow up a positive *in vitro* result showing chromosomal aberration. The MN test and CA test are able to detect chromosomal aberrations, whereas the comet assay is an indicator assay detecting putative DNA lesions. The transgenic rodent somatic and germ cell gene mutation assays ("TGR", OECD TG 488) and the *in vivo* comet Assay are suitable to follow up a positive *in vitro* result showing gene mutation. The TGR assay is able to detect gene mutations, whereas the comet assay is an indicator assay detecting putative DNA lesions.

According to the ECHA Guidance Chapter R.7a[4], the comet Assay is suitable to follow up the positive *in vitro* result for gene mutation and chromosomal aberrations. Therefore, this test is the most appropriate for the Substance.

According to the test method OECD TG 489, the test shall be performed in rats. Having considered the anticipated routes of human exposure and adequate exposure of the target tissue(s) performance of the test by the oral route is appropriate.

In line with the test method OECD TG 489, the test shall be performed by analysing tissues from liver as primary site of xenobiotic metabolism, glandular stomach and duodenum as sites of contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the Substance, and probable different local absorption rates of the Substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to analyse both tissues to ensure a sufficient evaluation of the potential for genotoxicity at the site of contact in the gastro-intestinal tract.

Germ cells

A subsequent germ cell genotoxicity study (TGR/OECD TG 488, or CA on spermatogonia/OECD TG 483) may still be required under Annex IX of REACH, in case 1) an *in vivo* genotoxicity test on somatic cell is positive, and 2) no clear conclusion can be made on germ cell mutagenicity.

> Therefore, you may consider to collect the male gonadal cells collected from the seminiferous tubules (as described by e.g. O'Brien *et al.*[5]) in addition to the other

[3] ECHA Guidance Chapter R.7a, Section R.7.7.6.3
[4] ECHA Guidance Chapter R.7a, Section R.7.7.6.3
[5] O'Brien, J.M., Beal, M.A., Gingerich, J.D., Soper, L., Douglas, G.R., Yauk, C.L., Marchetti, F. (2014) Transgenic Rodent Assay for Quantifying Male Germ Cell Mutant Frequency. J. Vis. Exp. (90), e51576, doi:10.3791/51576

aforementioned tissues, as it would optimise the use of animals. You can prepare the slides for male gonadal cells and store them for up to 2 months, at room temperature, in dry conditions and protected from light. Following the generation and analysis of data on somatic cells, in accordance to Annex IX, Section 8.4., column 2, you should consider analysing the slides prepared with gonadal cells. This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

Appendix C: 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.; test method OECD TG 414) in a second species (rat), oral route with the Substance

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

In your dossier, you have provided:

i. A key study [redacted] (1990), according to EPA OPP 83-3 (Prenatal Developmental Toxicity Study), in rabbit showing no developmental effects.
ii. A supporting study, Couri et al. (1982), showing no effects.
iii. A supporting study, Mobley et al. (1990), with 12 females rats/group showing significant decreases in exploratory activity in mid and high dose groups and significantly increased free T4 levels were in the high dose group.
iv. A supporting study, Moore et al. (1980), in mouse showing that the average weight of pups at weaning was significantly less in the treatment group compared to the control group. The average birth to weaning growth weight was similarly significantly less in the treatment group than in the control group. Decreased conception rate (percent of dams that were mated and also have live litters) was 39% in treated versus 56% in control.
v. A supporting study, Suh et al. (1983) in rats showing a significant dose-response relationship in the decreases of the numbers of implants and live foetuses in the ClO2 administered groups.
vi. A supporting study, Toth et al. (1990), showing reductions in pup's body weight on PND 11, 21 and 35 in ClO2 treated pups and decreases in absolute forebrain weight, without histology findings, and protein content on PND 21 and 35 with reduced DNA content only on PND 35.
vii. A supporting study, Taylor and Pfohl (1985), with chlorine dioxide in rat showing that rat pups exposed both pre-natally and post-natally from day 5 to day 20 of age, exhibited behavioural deficits and depresed brain growth , consistent with effects produced by depressed thyroid function.

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. OECD TG 414 requires that the following conditions are met (among others):

- Each test and control group should contain a sufficient number of females to result in approximately 20 female animals with implantation sites at necropsy. Groups with fewer than 16 animals with implantation sites may be inappropriate.
- All the structural skeletal and visceral malformations and other relevant alterations should be investigated.

In all these studies less animals (4 - 13 animals/sex/dose) than the minimum number specified by the OECD TG 414 were used. Furthermore, in the two studies (Toth et al. (1990) and Taylor and Pfohl (1985)) ranked with the highest reliability (2) among the provided studies, only limited parameters (brain and nervous system) were investigated compared to that required by OECD TG 414. In additon, none of these studies were

conducted according to GLP, or according to a testing guideline and limited documentation on the methodology used was provided.

Therefore the information provided does not fulfil the information requirement.

Information on study design

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 shall be performed in rat as preferred rodent species.

The study shall be performed with oral[6] administration of the Substance.

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

Appendix D: 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 18 January 2019.

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 took into account your comments and amended 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 E: Observations and technical guidance

1. The substance subject to the present decision is provisionally listed in the Community rolling action plan (CoRAP) for the start of substance evaluation in 2019.

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

3. 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.

4. 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'[7].

5. 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.

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

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"[8].

6. List of references of the ECHA Guidance and other guidance/ reference documents[9]

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)[10]

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[11]
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.

[8] https://echa.europa.eu/manuals
[9] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[10] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[11] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix F: 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.