EUROPEAN CHEMICALS AGENCY

~~Confidential~~

Helsinki, 12 May 2021

Addressees
Registrant(s) of JS_ Sodium ethylenesulphonate as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
28/04/2016

Registered substance subject to this decision ("the Substance")
Substance name: Reaction mass of disodium 2,2'-oxydiethanesulfonate and sodium ethenesulfonate
EC number: 700-978-5
CAS number: NS

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 in A.1, A.2., A.3, A.4., A.5., B.1. B.2., B.3. and C.1 below by ***21 November 2022*** and all other information listed below by ***20 November 2023***.

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

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

1. Skin sensitisation (Annex VII, Section 8.3.):

   i) in vitro/in chemico skin sensitisation information on molecular interactions with skin proteins (OECD TG 442C), inflammatory response in keratinocytes (OECD TG 442D) and activation of dendritic cells (OECD TG 442E) (Annex VII, Section 8.3.1.); and

   ii) in vivo skin sensitisation (Annex VII, Section 8.3.2.; test method: EU B.42./OECD TG 429), in case the in vitro/in chemico test methods specified under point i) are not applicable for the Substance or the results obtained are not adequate for classification and risk assessment

2. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: EU B.13/14. / OECD TG 471)

3. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: EU C.2./OECD TG 202)

4. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: EU C.3./OECD TG 201)

5. Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: OECD TG 301B/C/D/F or OECD TG 310)

B. Information required from all the Registrants subject to Annex VIII of REACH

1. In vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.; test method: OECD TG 473) or In vitro micronucleus study (Annex VIII, Section 8.4.2.; test method: OECD TG 487)

2. If negative results are obtained in tests performed for the information requirement of Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. then: In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490)

3. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: OECD TG 203)

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

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.; test method: OECD TG 408) by oral route, in rats

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat or rabbit)

3. Long-term toxicity testing on aquatic invertebrates (Annex IX, Section 9.1.5.; test method: EU C.20./OECD TG 211)

4. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: OECD TG 210)

D. Information required from 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) by oral route, in a second species (rat/rabbit)

Reasons for the requests are explained in the following appendices:

- Appendix entitled "Reasons common to several requests";
- Appendices entitled "Reasons to request information required under Annexes VII to X of REACH", respectively.

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.

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". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations 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.

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.

Appendix on Reasons common to several requests

1. Assessment of your read-across approach under Annex XI, Section 1.5.

You seek to adapt the following standard information requirements by applying a read-across approach in accordance with Annex XI, Section 1.5:

- Skin sensitisation, in vivo (Annex VII, Section 8.3.2)
- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

ECHA has considered the scientific and regulatory validity of your read-across approach(es) in general before assessing the specific standard information requirements in the following appendices.

Grouping of substances and read-across approach

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

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

A. Predictions for toxicological properties

You have not provided any read-across justification document in your registration dossier.

You read-across between the structurally similar substance, sodium ethylene sulphonate, EC No. 221-242-5 as source substance and the Substance as target substance.

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

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

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

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

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

Absence of read-across documentation

Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide a justification for the read-across including a hypothesis, explanation of the rationale for the prediction of properties and robust study summary(ies) of the source study(ies).[5]

You have provided studies conducted with other substances than your Substance in order to comply with the REACH information requirements. You have not provided documentation as to why this information is relevant for your Substance.

In the absence of such documentation, ECHA cannot verify that the properties of your Substance can be predicted from the data on the source substance(s).

B. Conclusions on the read-across approach

As explained above, you have not established that relevant properties of the Substance can be predicted from data on the analogue substance. Therefore, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. and your grouping and read-across approach is rejected.

2. Assessment of the identity of the test material

The following issue concerns the following information requirements:
- Skin sensitisation in vivo (Annex VII, Section 8.3.2)
- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- Ready biodegradability (Annex VII, Section 9.2.1.1.)
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

You have provided studies listed under each endpoint in appendices A-C that you claim were conducted with the Substance.

To comply with these information requirements, the test material in a study must be representative for the Substance (Art. 10 and Recital 19 of REACH; ECHA Guidance R.4.1).

Therefore, the unambiguous characterisation of the composition of the Substance and test material used to generate the data is required to evaluate the representativeness 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, and include details on the composition, including quantitative and qualitative information on all constituents present in the test material, or production process of the test material.

To identify the test materials you have provided the substance name, EC and/or CAS number, and/or the purity of the Substance in water. Information on the detailed composition, including quantitative and qualitative information on all constituents present in the test material, or production process of the test material has not been provided.

[5] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.6.1

Without comprehensive reporting of all constituents present in the test material (including their identity and concentrations) ECHA is unable to confirm that the test materials are representative of the Substance.

In your comments on the draft decision you provided information on the composition of test material in the Growth inhibition study aquatic plants and short-term toxicity testing on fish study. The information you have provided in your comments addresses the noncompliances identified in this section for these information requirements. However, as the information is currently not available in your registration dossier, this section still concerns these two information requirements. Also, there are other non compliances raised in the sections on these endpoints.

Therefore, the provided information is rejected.

Appendix A: Reasons to request information required under Annex VII of REACH

1. Skin sensitisation

Skin sensitisation is a standard information requirement in Annex VII, Section 8.3. to the REACH Regulation. Column 1 of Section 8.3. requires the registrants to submit information allowing a conclusion whether the substance is a skin sensitiser and whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A), and risk assessment, where required.

You have provided the following information in the technical dossier, based on which you conclude that the Substance is not a skin sensitiser.

i. In vivo Guinea Pig Maximization test (key study, OECD TG 406, 1988) with 30% aqueous solution of the Substance.

To fulfil the information requirement, as specified in the Annex VII, Section 8.3., Column 1 to the REACH Regulation, the following aspects must be covered: A) whether the Substance causes skin sensitisation, and B) whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A), in case, the Substance is considered to be a skin sensitiser.

A) Assessment whether the Substance causes skin sensitisation

You have provided an EU Method B.6/OECD TG 406 study according to the Guinea Pig Maximization test method.

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

To be considered compliant and enable concluding whether the Substance causes skin sensitisation, a study has to meet the requirements of the EU Method B.6/OECD TG 406. The key parameter(s) of this test guideline include appropriate dose level selection, number of animals and control groups:

a) Dose level selection rationale
b) The induction concentration should produce reactions to the skin and the challenge dose should be non-irritating (OECD TG 406, Test conditions, version of 12 May 1981).
c) Appropriate number of animals: minimum of 20 animals per dose group (OECD TG 406, Table 1, version of 12 May 1981).
d) Positive controls to establish the sensitivity and reliability of the experimental technique (OECD TG 406, Test procedure, version of 12 May 1981)

In the provided study:

a) Results of the range finding test were not provided
b) The concentration used for topical induction and challenge was the same i.e. 10% of test solution (test material 30% aqueous solution leading to corrected test item concentration of 3%), therefore the criteria for selecting topical induction (needs to produce skin reactions) and challenge (non-irritating) concentrations cannot be met.
c) 10 animals in test group and 5 animals in the control group were used.
d) No information on positive control group were provided.

Therefore the study does not fulfil the key parameter(s) set in the EU method B.6/OECD TG 406 and does not allow to make a conclusion whether the Substance causes skin sensitisation.

B) Assessment whether the Substance can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

In your comments on the draft decision you agree to this request.

As the currently available data does not allow to conclude whether the Substance causes skin sensitisation, this condition cannot be assessed.

To fulfil the information requirement for the Substance for skin sensitisation, *in vitro/in chemico* studies (OECD TG 442C, 442D and 442E) are considered suitable. In case *in vitro/in chemico* methods are not suitable for the Substance or the results cannot be used for classification and risk assessment an *in vivo* skin sensitisation study must be performed and the murine local lymph node assay (LLNA) (OEDC TG 429) is considered as the appropriate study.

2. In vitro gene mutation study in bacteria

An *in vitro* gene mutation study in bacteria is a standard information requirement in Annex VII to REACH.

You have provided a key study in your dossier:

i. *In vitro* gene mutation study in bacteria (1988) with 30% substance in water with the following strains, TA 98, TA 100, TA 1535, TA 1537, TA 1538 and E. coli WP2uvrA which all gave negative results.

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

Test material characterisation

As explained in Section 2 in the Appendix on Reasons common to several requests the test material characterisation does not fulfil the requirements of REACH. The study is therefore rejected.

In addition, the following endpoint-specific deficiency has been identified:

Test guideline key parameters

To fulfil the information requirement, the study has to meet the requirements of OECD TG 471 (1997). One of the key parameters of this test guideline includes:

a) The maximum dose tested must induce a reduction in the number of revertant colonies per plate compared to the negative control, or the precipitation of the tested substance. If no precipitate or limiting cytotoxicity is observed, the highest test dose must correspond to 5 mg/plate or 5 ml/plate.

The reported data for the study you have provided did not include:

a) a maximum dose of 5 mg/plate or 5 ml/plate or that induced a reduction in the number of revertant colonies per plate compared to the negative control, or the precipitation of the tested substance. The concentration of the test material was 30% and the resulting high dose in the mutagenicity test 1,667 µg/plate.

The information provided does not cover one of the key parameters required by OECD TG 471.

In your comments on the draft decision you agree to this request.

Therefore, the information requirement is not fulfilled.

To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471) is considered suitable.

3. Short-term toxicity testing on aquatic invertebrates

Short-term toxicity testing on aquatic invertebrates is a standard information requirement under Annex VII to REACH (Section 9.1.1.).

You have provided a key study (reliability score 1) according to OECD TG 202.

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

To fulfil the information requirement, a study must comply with the OECD TG 202 or the EU Method C.2 (Article 13(3) of REACH) and the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test. Therefore, the following requirements must be met:

- The test material identity is provided, including information on purity, presence of impurities and compositional information;
- The results can only be based on nominal or measured initial concentration if the concentration of the test material has been satisfactorily maintained within 20 % of the nominal or measured initial concentration throughout the test (see also ECHA Guidance R.7b, Section R.7.8.4.1);
- Adequate information on the analytical method (including performance parameters of the method) and on the results of the analytical determination of exposure concentrations are provided.

Considering that the reported constituents of the Substance are organic salts which are well soluble in water, the Substance (constituents of it) will be present in ionised forms at environmentally relevant pHs and possesses potential for adsorption to mineral components of environmental matrixes. Therefore it is expected that losses of the Substance, as compared to the nominal concentrations, will occur in aquatic toxicity tests during the exposure period and analytical monitoring of exposure concentrations throughout the test duration is necessary to confirm reliability of aquatic toxicity studies.

As explained in Appendix on Reasons common to several requests, identity of the test material in the key study is not sufficiently identified. Furthermore, information on the analytical method and results of the analytical determination of exposure concentrations throughout the test are not reported for this study.

In your comments on the draft decision you agree to this request.

On this basis, the information requirement is not fulfilled.

Study design

Due to its potential for adsorption, the Substance is difficult to test. OECD TG 202 specifies that, for difficult to test substances, you must consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 202.

4. Growth inhibition study aquatic plants

Growth inhibition study aquatic plants is an information requirement under Annex VII to REACH (Section 9.1.2).

You have provided key study (reliability score 1) according to OECD TG 201.

We have assessed this information and identified the following issues:

To fulfil the information requirement, a study must comply with OECD TG 201 and the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following requirements must be met:

- The test material identity is provided, including information on purity, presence of impurities and compositional information;The results of algal biomass determined in each flask at least daily during the test period are reported in a tabular form;
- The concentration series of the Substance (active ingredient) should preferably cover the range causing 5-75 % inhibition of algal growth rate or be up to limit concentration (100 mg/L or a concentration equal to the limit of solubility whichever is lower).

As explained in Appendix on Reasons common to several requests, identity of the test material in the key study based on your comments to the draft decision is now sufficiently identified but the information is currently not available in your registration dossier. Furthermore, information on algal biomass in each flask throughout the test duration which would allow confirmation of fulfilment of validity criteria is not provided.

Effect concentrations are not expressed based on exposure concentrations of the Substance (active ingredient), but on the test material which contains 25.09% of the tested substance and the concentration series used in the test neither cover the range causing 5-75 % inhibition of algal growth rate nor the Substance (active ingredient) was tested up to limit concentration. In your comments on the draft decision you explain that no biomass concentrations were determined as the substance tend to polymerize upon heating and as a consequence cell count were measured instead. You also refer to the OECD TG 201 that "*a limit test involving a comparison of responses in a control group and one treatment group (100 mg/L or a concentration equal to the limit of solubility), may be undertaken* ". You note that a growth inhibition of 88.47 % was observed at 100 mg/L test concentration and the Substance has an aqueous solubility of >1000 g/L at 20°C, which is no longer realistic for testing. Finally, you refer to the predicted by QSAR values of Koc (organic carbon normalized adsorption coefficient) of the most components (constituents and impurities) of the Substance and summarise that these values of Koc indicate the main constituents and impurities of the Substance have a negligible sorption to soil and sediment.

OECD TG 201 indicates that algal biomass is defined as the dry weight per volume, e.g. mg algae/litre test solution. However, dry weight is difficult to measure and therefore surrogate parameters are used. Of these surrogates, cell counts are most often used. Other surrogate parameters include cell volume, fluorescence, optical density, etc. A conversion factor between the measured surrogate parameter and biomass should be known. Thus, even surrogate parameter was used, the estimated biomass in each flask at least daily during the test period must be reported in a tabular form in order to allow to conduct an independent assessment of the study reliability. Furthermore, as the surrogate parameter is used for the biomass estimation, a satisfactory correlation with biomass must be demonstrated for the method used to count cells over the range of biomass occurring in the test.

In the registration dossier in the "Test material information" section of the study summary you indicated that the analytical purity of the test material is 25.09%, i.e. test material

contains 25.09% of the tested substance. Thus, the highest nominal concentration of the test material of 100 mg/l, contained app. 25 mg/l of the tested substance, i.e. concentration series used were not up to the limit concentration of 100 mg/l of the Substance. Furthermore, ErC50 (concentration causing 50 % inhibition of algal growth rate) reported in the registration dossier is above 55.95 mg/l, i.e. the concentration causing 50% inhibition of algal growth rate was not reached and definite value of ErC50 could not be estimated.

As noted in the Section A.3 above the Substance (constituents of it) will be present in ionised forms at environmentally relevant pHs. ECHA Guidance, R.7b (Table R.7.8-2) notes that ionised substances might be lost from the test system as "*bind to substrates of opposite charge e.g.cationically charged substances bind to negatively charged humic acids, clay, glassware, microorganisms etc; anionic compounds bind to positively charged Si, Al or Fe oxide*". Thus, constituents of the Substance possess potential for adsorption to mineral components of environmental matrixes and to substrates of opposite charge of the test system. Furthermore, ECHA Guidance, R.7a (section R.7.1.15.4) explains that "*A measured adsorption coefficient is usually needed for ionising substances, since it is important to have information on pH-dependence*".

On this basis, the information requirement is not fulfilled.

Study design

OECD TG 201 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Section on Short-term toxicity testing on aquatic invertebrates.

5. Ready biodegradability

Ready biodegradability is a standard information requirement under Annex VII to REACH (Section 9.2.1.1.).

You have provided key study (reliability score 2) according to OECD TG 301E.

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

To comply with this information requirement, a study must fulfil the requirements of the corresponding OECD test guideline or EU method (Article 13(3) of REACH), in this case OECD TG 301E. Therefore, the following requirements must be met:

- The test material identity is provided, including information on purity, presence of impurities and compositional information (if applicable);
- The OECD TG 301E is not applicable to adsorbing substances unless appropriate adsorption control are included in the test design; when the substance is suspected to be adsorptive, a preliminary assessment of the extent of adsorption must be conducted using an adsorption control (*i.e.* containing the test substance, inoculum and sterilising agent);
- The dilution water does not contain more than 10% of the organic carbon content introduced by the test material;
- The inoculum is not be pre-adapted to the test substance;
- The concentration of the inoculum is set to reach a bacterial cell density of approx. 10^5 cells/L in the test vessel. The concentration of added inoculum is ≤ 0.5 mL/L;
- The concentration of the test substance is in the range of 10-40 mg DOC/L.

As explained under Section on Short-term toxicity testing on aquatic invertebrates above, the Substance (constituents of it) will be present in ionised forms at environmentally relevant pHs

and possesses potential for adsorption to mineral components of environmental matrixes.

As explained in Appendix on Reasons common to several requests, identity of the test material in the key study is not sufficiently identified. Furthermore, the information to verify fulfilment of other above listed requirements is missing.

In your comments on the draft decision you agree to this request.

On this basis, the information requirement is not fulfilled.

Appendix B: Reasons to request information required under Annex VIII of REACH

1. In vitro cytogenicity study in mammalian cells or In vitro micronucleus study

An *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study is a standard information requirement in Annex VIII to REACH.

You have provided two records for the same key study in your dossier:

i. *In vitro* cytogenicity / chromosome aberration study (1999) with 25% substance in water, with the analogue substance sodium ethenesulfonate (EC 221-242-5)

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

Grouping and read-across rejected

As explained in section 1 in the Appendix on Reasons common to several requests your adaptation is rejected.

Test material characterisation

As explained in section 2 in the Appendix on Reasons common to several requests the test material characterisation for the study that you claim was conducted with the Substance does not fulfil the requirements of REACH. The study is thus rejected. In addition, the following deficiencies have been identified :

Test guideline key parameters

To fulfil the information requirement, the study has to be an *in vitro* chromosomal aberration test or an *in vitro* micronucleus test, conducted in mammalian cells in accordance with OECD TG 473 or OECD TG 487, respectively[6]. The key parameters of these test guidelines include:

a) At least 300 well-spread metaphases must be scored per concentration.
b) The response for the concurrent negative control must be inside the historical control range of the laboratory.
c) Data on the cytotoxicity and the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures must be reported.

The reported data for the study you have provided did not include:

a) the scoring of at least 300 metaphases per concentration.
b) a negative control with a response inside the historical control range of the laboratory.
c) data on the cytotoxicity and/or the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures.

The information provided does not cover key parameters required by the relevant OECD TG.

In your comments on the draft decision you agree to this request.

Therefore, the information requirement is not fulfilled.

To fulfil the information requirement for the Substance, both *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) and *in vitro* micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) are considered suitable.

[6] ECHA Guidance R.7a, Table R.7.7-2, p.557

2. Only if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained, In vitro gene mutation study in mammalian cells

An *in vitro* gene mutation study in mammalian cells is a standard information requirement in Annex VIII to REACH in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

For Annex VIII, 8.4.3., you have provided a study in your dossier.

Your dossier contains data for an *in vitro* gene mutation study in bacteria, and data for an in vitro cytogenicity study in mammalian cells or *in vitro* micronucleus study.

The information for the *in vitro* gene mutation study in bacteria and for the *in vitro* cytogenicity study in mammalian cells provided in the dossier are rejected for the reasons provided in sections A.1 and B.1 of Appendices A and B.

The result of the requests for information in sections A.1 and B.1 of Appendices A and B will determine whether the present requirement for an *in vitro* mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3 is triggered.

You have provided a key study in your dossier:

i. *In vitro* gene mutation study in mammalian cells (1997) with 25% substance in water, with the analogue substance sodium ethenesulfonate (EC 221-242-5)

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

Grouping and read-across rejected

As explained in section 1 in the Appendix on Reasons common to several requests your adaptation is rejected.

Test guideline key parameters

To fulfil the information requirement, the *in vitro* gene mutation study on mammalian cells has to meet the requirements of OECD TG 476 or OECD TG 490. The key parameter(s) of these test guidelines include:

a) At least 4 concentrations must be evaluated, in each test condition.
b) The response for the concurrent negative control must be inside the historical control range of the laboratory.
c) Data on the cytotoxicity and the mutation frequency for the treated and control cultures must be reported.

The reported data for the study you have provided do not include:

a) the evaluation of at least 4 concentrations in each test condition.
b) a negative control with a response inside the historical control range of the laboratory.
c) data on the cytotoxicity and the mutation frequency for the treated and control cultures.

The information provided does not cover key parameter(s) required by the relevant OECD TG.

In your comments on the draft decision you agree to this request.

Therefore, the information requirement is not fulfilled.

Consequently, you are required to provide information for this endpoint, if the *in vitro* gene

mutation study in bacteria and the *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study provide a negative result.

To fulfil the information requirement for the Substance, both the *in vitro* mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) and the thymidine kinase gene (OECD TG 490) are considered suitable.

3. Short-term toxicity testing on fish

Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.).

You have provided a key study (reliability score 1) according to OECD TG 203.

We have assessed this information and identified the following issues:
To fulfil the information requirement, a study must comply with OECD TG 203 and the requirements of OECD GD 23 (ENV/JM/MONO(2000)6/REV1) if the substance is difficult to test (Article 13(3) of REACH). Therefore, the following requirements must be met:

- The test material identity is provided, including information on purity, presence of impurities and compositional information;adequate information on the analytical method (including performance parameters of the method) and on the results of the analytical determination of exposure concentrations are provided;
- the concentration series of the Substance (active ingredient) should be up to limit concentration (100 mg/L or a concentration equal to the limit of solubility).

As explained under Section on Short-term toxicity testing on aquatic invertebrates above, the Substance (constituents of it) will be present in ionised forms at environmentally relevant pHs and possesses potential for adsorption to mineral components of environmental matrixes. Therefore it is expected that losses of the Substance, as compared to the nominal concentrations, will occur in aquatic toxicity tests during the exposure period and analytical monitoring of exposure concentrations throughout the test duration is necessary to confirm reliability of aquatic toxicity studies.

As explained in Appendix on Reasons common to several requests, identity of the test material in the key study based on your comments to the draft decision is now sufficiently identified but the information is currently not available in your registration dossier. Furthermore, information on results of the analytical determination of exposure concentrations throughout the test is not reported for the key study. Finally, effect concentrations are not expressed based on exposure concentrations of the Substance (active ingredient) and the Substance (active ingredient) was not tested up to limit concentration in the key study.

In your comments on the draft decision you explain that the key study "*was conducted under semi-static conditions where test solutions were renewed at pre-defined periods (after every 24 hours) during the study. This helps to maintain stable test concentrations for the substance during the duration of the study.*" Furthermore, for the constituents of the Substance you note that "*only the ionic forms are present*" at environmentally relevant pHs. You refer to the predicted by QSAR values of Koc of the most components (constituents and impurities) of the Substance and summarise that these values of Koc indicate that the main constituents and impurities of the Substance have a negligible sorption to soil and *"as a consequence the test concentration for the substance during the duration of the study has been maintained"*.

As explained in the Section A.4 above the Substance (constituents of it) will be present in ionised forms at environmentally relevant pHs. ECHA Guidance, R.7b (Table R.7.8-2) notes that ionised substances might be lost from the test system as "*bind to substrates of opposite charge e.g.cationically charged substances bind to negatively charged humic acids, clay,*

glassware, microorganisms etc; anionic compounds bind to positively charged Si, Al or Fe oxide". Thus, constituents of the Substance possess potential for adsorption to mineral components of environmental matrixes and to substrates of opposite charge of the test system. Furthermore, ECHA Guidance, R.7a (section R.7.1.15.4) explains that "*A measured adsorption coefficient is usually needed for ionising substances, since it is important to have information on pH-dependence*".

According to OECD TG 203 analytical measurement of test concentrations is compulsory. It notes that in semi-static tests, test concentrations are measured at least twice over one exposure period (before and after renewal of test solutions). If the concentrations of the test material:

- are expected to remain within ± 20 % of the nominal, then the test substance concentration is determined) in the highest and lowest test concentrations, and a concentration around the expected LC50;
- are expected to decline by more than 20%, analytical monitoring is conducted on all test concentrations with an additional determinations on the other exposure period(s).

As information on results of the analytical determination of exposure concentrations throughout the test duration is not reported for the key study, an independent assessment of the study reliability is not possible.

On this basis, the information requirement is not fulfilled.

Study design

OECD TG 203 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Section on Short-term toxicity testing on aquatic invertebrates.

Appendix C: Reasons to request information required under Annex IX of REACH

1. Sub-chronic toxicity study (90-day)

A Sub-chronic toxicity study (90 day) is a standard information requirement in Annex IX to REACH.

You have provided a key study for this endpoint in your dossier:
Combined sub-acute repeated dose-toxicity and screening for reproductive/developmental toxicity study (2010, OECD TG 422) with 25% substance in water

Test material characterisation

As explained in Section 2 in the Appendix on Reasons common to several requests the test material characterisation does not fulfil the requirements of REACH. The study is therefore rejected. In addition, the following endpoint-specific deficiencies have been identified:

Test guideline key parameters

To be considered compliant and enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL), a study has to meet the requirements of OECD TG 408. The following key parameter(s) of this test guideline include, among others

- The highest dose level should aim to induce some systemic toxicity, but not death or severe suffering, or be tested up to a limit dose of 1000 mg/kg bw/d of the Substance;
- At least 10 female and 10 male animals should be used at each dose level (including control group);
- Dosing of the Substance daily for a period of 90 days until the scheduled termination of the study.

The highest dose level in the study did not induce any systemic toxicity. Therefore, the dose level selection was too low, and the study does not fulfil the criterion set in OECD TG 408.

The Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) you have submitted does not have the required exposure duration of 90 days as required in OECD TG 408, because the exposure duration of the screening test as you reported is 39-47 days (for females) and 28 days (for males). Furthermore the organ weight and histopathological investigations in OECD TG 422 are only conducted using 5 animals per sex per group and not 10 per sex per group as in OECD TG 408.

In your comments on the draft decision you agree to this request.

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

Information on the design of the study to be performed

Referring to the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity, because the substance is a liquid of very low vapour pressure and no uses with spray application are reported that could potentially lead to aerosols of inhalable size.

Therefore the sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration of the Substance

2. Pre-natal developmental toxicity study in one species

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

You have provided an adaptation according to Annex X Setion 8.7 Column 2 for this endpoint in your dossier:

"According Column 2 of Annex X of the REACH regulation the study does not need to be conducted if" [...] *"All tests performed [...] show no toxicological activity so far, the repeated dose test does not give any concern that systemic absorption would occur and no significant exposure to humans is expected."*

According to Annex IX, Section 8.7., Column 2, third indent, the study does not need to be conducted if the substance is of low toxicological activity. This needs to be demonstrated with three concomitant criteria, namely:

- that there is no evidence of toxicity seen in any of the tests available; and
- that it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure; and
- that there is no or no significant human exposure.

In your adaptation, you have not substantiated your claim on no toxicity: Although there is no evidence of toxicity in the available repeated dose toxicity study, the submitted study is rejected due to the unconfirmed test material identity, and because the highest dose used in this study was not the limit dose (1000 mg/kg bw/day). Additionally, this is only a short-term study (28-47 days exposure). In addition, you have not provided any toxicokinetic data to show that there is no systemic absorption. Furthermore, the uses of the Substance indicate that there is significant human exposure e.g. through (non-)industrial spraying application.

In your comments on the draft decision you agree to this request.

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

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[7] administration of the Substance.

3. Long-term toxicity testing on aquatic invertebrates

Long-term toxicity testing on aquatic invertebrates is an information requirement under Annex IX to REACH (Section 9.1.5.).

You have adapted this information requirement based on Annex IX, Section 9.1., Column 2, stating that "*According Column 2 of Annex IX of REACH regulation reports that long-term testing shall be proposed if the chemical safety assessment (CSA) according Annex I indicates the need to investigate further the effects on aquatic organisms. This test does not need to be conducted since no CSA needs to be performed for SVS because the substance is not classified and no exposure is needed.*"

Under Section 9.1., Column 2, Annex IX to REACH, the study may be omitted if the CSA demonstrates that risks towards the aquatic compartment arising from the manufacture and use of the substance are controlled (Annex I, Section 0.1). The justification for this adaptation must be documented in the Chemical Safety Report (CSR) and include all the following elements:

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

- the predicted no effect concentrations (PNEC) for the aquatic compartment which must be based on:
  - reliable information on the hazardous properties of the Substance on at least three trophic levels,
  - an appropriate assessment factor (AF) (ECHA Guidance R.10, Section R.10.3),
- a quantitative exposure assessment which leads to derivation of predicted environmental concentrations (PECs),
- the outcome of the risk characterisation ratio (RCR) which demonstrates that the risks are adequately controlled (*i.e.* PEC < PNEC).

As concluded in the respective sections above and below, the information requirements for the short-term toxicity testing on aquatic invertebrates, growth inhibition study aquatic plants and for the short- and long-term toxicity testing on fish are not fulfilled. Hence your dossier currently does not include adequate information for the Substance on at least three trophic levels to characterize the hazard property (aquatic toxicity) of the Substance.

Therefore, a reliable PNEC cannot be derived and your CSA does not demonstrate that the risks of the Substance are adequately controlled. As a consequence, your adaptation is rejected as it does not meet the specific rules for adaptation of Annex IX, Section 9.1., Column 2.

In your comments on the draft decision you agree to this request.

Thus, the information requirement is not fulfilled.

Study design

OECD TG 211 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Section on Short-term toxicity testing on aquatic invertebrates.

4. Long-term toxicity testing on fish

Long-term toxicity testing on fish is an information requirement under Annex IX to REACH (Section 9.1.6.).

You have adapted this information requirement based on Annex IX, Section 9.1., Column 2, stating that "*According Column 2 of Annex IX of REACH regulation reports that long-term testing shall be proposed if the chemical safety assessment (CSA) according Annex I indicates the need to investigate further the effects on aquatic organisms. This test does not need to be conducted since no CSA needs to be performed for SVS because the substance is not classified and no exposure is needed.*"

Under Section 9.1., Column 2, Annex IX to REACH, the study may be omitted if the CSA demonstrates that risks towards the aquatic compartment arising from the manufacture and use of the substance are controlled (Annex I, Section 0.1). The justification for this adaptation must be documented in the CSR and include all the following elements:

- PNEC for the aquatic compartment which must be based on:
  - reliable information on the hazardous properties of the Substance on at least three trophic levels,
  - an appropriate assessment factor (AF) (ECHA Guidance R.10, Section R.10.3),
- a quantitative exposure assessment which leads to derivation of PECs,
- the outcome of RCR which demonstrates that the risks are adequately controlled (*i.e.* PEC < PNEC).

As concluded in the respective sections above, the information requirements for the short- and long-term toxicity testing on aquatic invertebrates, growth inhibition study aquatic plants and for the short-term toxicity testing on fish are not fulfilled. Hence your dossier currently does not include adequate information for the Substance on at least three trophic levels to characterize the hazard property (aquatic toxicity) of the Substance.

Therefore, a reliable PNEC cannot be derived and your CSA does not demonstrate that the risks of the Substance are adequately controlled. As a consequence, your adaptation is rejected as it does not meet the specific rules for adaptation of Annex IX, Section 9.1., Column 2.

In your comments on the draft decision you agree to this request.

Thus, the information requirement is not fulfilled.

Study design

To fulfil the information requirement for the Substance, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (ECHA Guidance R.7.8.2.).

OECD TG 210 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Section on Short-term toxicity testing on aquatic invertebrates.

Appendix D: Reasons to request information required under Annex X of REACH

1. Pre-natal developmental toxicity study 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.

You have provided an adaptation according to Annex X Setion 8.7 Column 2 for this endpoint in your dossier:

"According Column 2 of Annex X of the REACH regulation the study does not need to be conducted if" [...] *"All tests performed [...] show no toxicological activity so far, the repeated dose test does not give any concern that systemic absorption would occur and no significant exposure to humans is expected."*

You have not provided information on a second species. 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.

According to Annex IX, Section 8.7., Column 2, third indent, the study does not need to be conducted if the substance is of low toxicological activity. This needs to be demonstrated with three concomitant criteria, namely:

- that there is no evidence of toxicity seen in any of the tests available; and
- that it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure; and
- that there is no or no significant human exposure.

In your adaptation, you have not substantiated your claim on no toxicity: Although there is no evidence of toxicity in the available repeated dose toxicity study, the submitted study is rejected due to the unconfirmed test material identity, and because the highest dose used in this study was not the limit dose (1000 mg/kg bw/day). Additionally, this is only a short-term study (28-47 days exposure). In addition, you have not provided any toxicokinetic data to show that there is no systemic absorption. Furthermore, the uses of the Substance indicate that there is significant human exposure e.g. through (non-)industrial spraying application.

In your comments on the draft decision you agree to this request.

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

Information on study design

A PNDT study according to the OECD TG 414 study should be performed in the rabbit or rat as the preferred second species, depending on the species tested in the first PNDT study (request C.2 in this decision).

The study shall be performed with oral[8] administration of the Substance.

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

Appendix E: 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[9].

B. Test material

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 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.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[10].

[9] https://echa.europa.eu/practical-guides
[10] https://echa.europa.eu/manuals

Appendix F: General recommendations when conducting and reporting new tests for REACH purposes

A. Testing strategy for aquatic toxicity testing

You are advised to consult ECHA Guidance R.7b, (Section R.7.8.5) which describes the Integrated Testing Strategy, to determine the sequence of aquatic toxicity tests and testing needed.

Appendix G: Procedure

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

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

The compliance check was initiated on 10 April 2019.

The decision making followed the procedure of Article 51 of the REACH Regulation, as described below:

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) but amended the deadlines.

Deadline to submit the requested information in this decision

The timelines indicated in the initial draft decision to provide the information requested is as follows:

- you must submit the information listed in A.1, A.2., B.1. B.2., C.1 below by ***exact date – 12 months from the date of the decision*** and all other information listed below by ***exact date – 24 months from the date of the decision***.

In your comments on the draft decision, you requested an extension of the timelines from 12 to 18 months "*for annex VII, VIII, including OECD 408*" and from 24 to 30 months "*for OECD 414, 211, 210 and 414 second species*". You justified your request with the following arguments, which ECHA has evaluated:

- Based on the need to develop and validate a new and suitable analytic method for the constituents of the substance by the CRO prior to starting the requested studies, the lead registrant strongly requests to add 6 months additional time to all testing requirements for both deadlines.

- In addition to the low log Koc value, you propose to further investigate the predicted low potential for adsorption of the test substance by measuring of log D (at three different pH's) prior to the start of the studies.

There is no request for a study to investigate adsorption in this draft decision. Such a study, if relevant, could be performed at any time by you. You justify that you foresee specific technical developmental aspects required for the analysis of the Substance. Therefore, ECHA partly considers that the need to extend the deadlines of this draft decision is justified. The draft decision deadlines have been amended from 12 to 18 months for A.1, A.2., A.3, A.4., A.5., B.1., B.2., B.3. and C.1., and from 24 to 30 months for C.2., C.3., C4., and D.1 from the date of the 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 H: List of references - ECHA Guidance[11] 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)[12]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)

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[13]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

[11] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[12] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[13] 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 I: 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]

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.