~~Confidential~~

Helsinki, 10 November 2023

Addressee(s)
Registrant(s) of JS_AOS(even numbered) as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
19 December 2018

Registered substance subject to this decision ("the Substance")
Substance name: Sulfonic acids, C14-16 (even numbered)-alkane hydroxy and C14-16 (even numbered)-alkene, sodium salts
EC/List number: 931-534-0

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by ***15 February 2027***.

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

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

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

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

2. *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: EU B.17./OECD TG 476 or EU B.67./OECD TG 490).

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

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: EU C.47./OECD TG 210).

Information required from all the Registrants subject to Annex X of REACH

5. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route, specified as follows:
    - At least ten weeks premating exposure duration for the parental (P0) generation;
    - The highest dose level in P0 animals must be determined based on clear evidence of an adverse effect on sexual function and fertility without severe suffering or deaths in P0 animals as specified further in Appendix 1, or follow the limit dose concept. The reporting of the study must provide the justification for the setting of the dose levels;
    - Cohort 1A (Reproductive toxicity); and

- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.

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

The reasons for the request(s) are explained in Appendix 1.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressees of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

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

How to comply with your information requirements

To comply with your information requirements, you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also **update the chemical safety report, where** relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general requirements for testing and reporting new tests under REACH, see Appendix 4.

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 Mike Rasenberg, Director of Hazard Assessment

Appendix 1: Reasons for the request(s)
Appendix 2: Procedure
Appendix 3: Addressees of the decision and their individual information requirements
Appendix 4: Conducting and reporting new tests under REACH

[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 1: Reasons for the request(s)

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Reasons related to the information under Annex VII of REACH

1. Growth inhibition study aquatic plants

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

1.1. Information provided

2 You have provided:

(i) Growth inhibition study on algae (1997) with the Substance;

(ii) Growth inhibition study on algae (1984) with the Substance.

1.2. Assessment of the information provided

1.2.1. Study not conducted according to GLP

3 (Eco)toxicological studies must comply with GLP or another recognised international standard; Art. 13(4) of REACH.

4 You have indicated that study (ii) is "not GLP-compliant", without further explanation.

5 The test does not comply with GLP or another recognised international standard and is therefore rejected.

1.2.2. The provided studies do not meet the specifications of the test guideline(s)

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

Validity criteria

a) exponential growth in the control cultures is observed over the entire duration of the test;
b) at least 16-fold increase in biomass is observed in the control cultures by the end of the test;
c) the mean coefficient of variation for section-by-section specific growth rates (days 0-1, 1-2 and 2-3, for 72-hour tests) in the control cultures is ≤ 35%;
d) the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures is ≤ 7% in tests with [Pseudokirchneriella subcapitata / Desmodesmus subspicatus]. For other less frequently tested species, the value is ≤ 10%;

Technical specifications impacting the sensitivity/reliability of the test

e) three replicates at each test concentration and at least three replicates for controls are included;
f) one of the two alternative growth medium (*i.e.* the OECD or the AAP medium) is used. Any deviations from recommended test media must be described and justified;
g) for *Raphidocelis subcapitata* (formerly *Pseudokirchneriella subcapitata*) the initial cell density is 5 x 10^3- 10^4 cells/mL, not exceeding 0.5 mg dry weight/L;
h) the pH of the control medium does not increase by > 1.5 units;
i) the test concentrations are arranged in a geometric series with a spacing factor ≤ 3.2, unless a higher factor is justified by a flat concentration response curve;

Characterisation of exposure

j) analytical monitoring must be conducted. Alternatively, a justification why the analytical monitoring of exposure concentrations is not technically feasible must be provided;
k) the results can be based on nominal or measured initial concentration only if the concentration of the test material has been maintained within ±20 % of the nominal or measured initial concentration throughout the test;
l) if the concentration of the test material has not been maintained within ±20 % of the nominal or measured initial concentration throughout the test, results must be based on the geometric mean of measured concentrations during exposure or on a model describing the decline of the concentration of the test material over the exposure period.

7 In study (i) :

Technical specifications impacting the sensitivity/reliability of the test

e) the number of replicates was 2 in each test concentration and 1 in the control;
f) the test medium is described as ISO growth medium without justification;

Characterisation of exposure

j) no analytical monitoring of exposure was conducted;
k) and l) You have expressed the effect values based on nominal concentrations. You have provided no data to demonstrate that the concentration of the test material was within ± 20 % of nominal concentrations throughout the test;

8 Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study results. In particular, no information on an adequate analytical method and analytical measurement is available, which may result in an underestimation of aquatic toxicity. Available information on the test medium does not allow an assessment of its suitability for the test;

9 On this basis, the specification(s) of OECD TG 201 are not met.

10 In study (ii) :

Validity criteria

a) exponential growth in the control cultures was provided only for the entire test period. No information for daily growth was provided nor raw data in the registration dossier;

b) the biomass at the start of the test was 0.7 mg dry weight/L but no information on the biomass at the end of the test is reported;

c) the mean coefficient of variation for section-by-section specific growth in the control was not provided nor raw data in the registration dossier;

d) the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures was not provided nor raw data in the registration dossier;

Technical specifications impacting the sensitivity/reliability of the test

f) the test medium is described as modified Hughes, Gorham and Zehnder's medium No. 11. You have not provided a justification as to why you did not use one of the two alternative growth medium of OECD TG 201;
g) the test was conducted on *Raphidocelis subcapitata* and the initial cell density was 0.7 mg dry weight/L;

h) the pH increase in the controls is not reported;
i) no information on the test concentrations is reported in the dossier;

Characterisation of exposure

j) no analytical monitoring of exposure was conducted;
k) and l) You have expressed the effect values based on nominal concentrations. You have provided no data to demonstrate that the concentration of the test material was within ± 20 % of nominal concentrations throughout the test.

11 Based on the above,

- the validity criteria of OECD TG 201 are not met
- there are critical methodological deficiencies resulting in the rejection of the study results. More specifically no analytical measurements have been conducted, therefore it is not possible to verify that the exposure of tested organisms to the Substance has been maintained through the study, which may result in an underestimation of aquatic toxicity; the initial cell density is higher than that required in the OECD TG 201, this can affect the exponential growth through the incubation period due to the risk of nutrient depletion [and therefore affect the obtained toxicity values?]; it was not demonstrated that the pH was maintained in the acceptable interval reported in the OECD TG 201, this can impact on the growth in the control and therefore on the obtained toxicity values.

12 On this basis, the specification(s) of OECD TG 201 are not met.

13 Therefore, the information requirement is not fulfilled.

1.3. Study design

14 The Substance is difficult to test due to the low surface tension (36.1 mN/m). OECD TG 201 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 201. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

15 For multi-constituents/UVCBs, the analytical method must be adequate to monitor qualitative and quantitative changes in exposure to the dissolved fraction of the test material during the test (e.g. by comparing mass spectral full-scan GC or HPLC chromatogram peak areas or by using targeted measures of key constituents or groups of constituents).

16 If you decide to use the Water Accommodated Fraction (WAF) approach, in addition to the above, you must:

- use loading rates that are sufficiently low to be in the solubility range of most constituents (or that are consistent with the PEC value). This condition is mandatory to provide relevant information for the hazard and risk assessment (Guidance on IRs and CSA, Appendix R.7.8.1-1, Table R.7.8-3);
- provide a full description of the method used to prepare the WAF (including, among others, loading rates, details on the mixing procedure, method to

separate any remaining non-dissolved test material including a justification for the separation technique);

- prepare WAFs separately for each dose level (*i.e.* loading rate) and in a consistent manner.

17 In your comments on the initial draft decision you agree to conduct the study.

Reasons related to the information under Annex VIII of REACH

2. *In vitro* gene mutation study in mammalian cells

18 An in vitro gene mutation study in mammalian cells is an information requirement under Annex VIII, Section 8.4.3., in case of a negative result in the in vitro gene mutation test in bacteria and the in vitro cytogenicity test.

2.1. Triggering of the information requirement

19 Your dossier contains negative results for both an Ames test and an in vitro cytogenicity study.

20 Therefore, the information requirement is triggered.

2.2. Information provided

21 ECHA understands that you have provided an in vitro OECD 476 study (1994) with the Substance to fulfil this information requirement, although it is identified as a cytogenicity study.

22 ECHA understands that you have also adapted this information requirement by using Annex VIII, Section 8.4., Column 2. To support the adaptation, you have provided a weight of evidence approach relying on the following information:

2.3. Assessment of the information provided

2.3.1. In vitro study

23 Under Article 10(a)(vii) and Annex I, Section 1.1.4, a robust study summary is required for a study intended to fulfil this information requirement.

24 A robust study summary must provide a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study (Article 3(28)).

25 You have provided only the name of the study (i.e. in vitro OECD 476 study (1994)), but you have not provided a robust study summary with detailed information on the methods, results and conclusions.

26 Then, the study record misses several essential pieces of information and does not allow for an independent assessment of each source of information and contributing to the overall weight of evidence for the information requirement under consideration.

27 Therefore, the study is rejected.

2.3.2. Column 2 adaptation

28 ECHA has assessed your weight of evidence approach based on the criteria set under Annex XI Section 1.2 of REACH which can be applied by analogy to assess the validity of your weight of evidence approach.

29 Annex XI, Section 1.2. states that there may be sufficient weight of evidence from several independent sources of information enabling, through a reasoned justification, a conclusion on the information requirement, while the information from each single source alone is insufficient to fulfil the information requirement.

30 The justification must have regard to the information that would otherwise be obtained from the study that must normally be performed for this information requirement.

31 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 on the corresponding information requirement.

2.3.2.1. Lack of documentation justifying the weight of evidence adaptation

32 Annex XI, Section 1.2. requires that adequate and reliable documentation is provided to describe a weight of evidence approach. This documentation must include robust study summaries of the studies used as sources of information and a justification explaining why the sources of information together provide a conclusion on the information requirement.

33 You have not included a justification for your weight of evidence adaptation, which would include an adequate and reliable (concise) documentation as to why the sources of information provide sufficient weight to conclude on the information requirements under consideration.

2.3.2.2. Missing robust study summaries

34 Annex XI, Section 1.2. requires that whenever weight of evidence is used adequate and reliable documentation of the applied method must be provided. Such documentation must include a robust study summary for each source of information used in the adaptations.

35 A robust study summary must provide a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study (Article 3(28)).

36 In addition, for weight of evidence adaptations, the robust study summary must clearly indicate which key parameters of the study normally required for the information requirement are investigated in the study.

37 For all three sources of information, you have provided only the name of the study, but you have not provided information on the methods, results and conclusions, except the doses, the species, the route of administration, the type of cells treated, as well as, in one case a short text under additional informations not related to tests with mammalian cells.

38 This information does not allow for an independent assessment of each source of information and contributing to the overall weight of evidence for the information requirement under consideration.

2.3.2.3. Relevance of the studies

39 In addition to the critical deficiencies identified above, ECHA identified specific issue(s) addressed below.

40 Information that can be used to support weight of evidence adaptation for the information requirement of Annex VIII, Section 8.4.3 includes similar information that is produced by OECD 476 / 490 with a design as specified in this decision.

41 This includes:

- Detection and quantification of gene mutations (point mutations, frame-shift mutations, small deletions, etc.) including data on the frequency of mutant colonies in cultured mammalian cells (*in vitro*) or mutant frequency for each tissue in mammals (*in vivo*).

42 The information provided contain information on "Injected bacteria or yeast cells". None of the sources (i)-(iii) provide information on mammalian cells.

43 Moreover, you have assigned a reliability score 4 to the provided studies (i)-(iii). ECHA agrees on this.

44 ECHA concludes that you have failed to provide a weight of evidence justification and a robust study summary for each source study used in the adaptation as required by Annex XI, Section 1.2 and, in any cases, these source studies provide no information on Detection and quantification of gene mutations (point mutations, frame-shift mutations, small deletions, etc.) including data on the frequency of mutant colonies in cultured mammalian cells (in vitro) or mutant frequency for each tissue in mammals (in vivo).

45 Therefore, it is not possible to conclude, based on any source of information alone or considered together, on the information requirement for in vitro gene mutation in mammalian cells and your adaptation is rejected.

2.4. Study design

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

47 In your comments on the initial draft decision you indicate that you will consider the possibility to update your adaptation before conducting a new study.

Reasons related to the information under Annex IX of REACH

3. Long-term toxicity testing on aquatic invertebrates

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

3.1. Information provided

49 You have provided:

(i) a long-term toxicity study on *Daphnia magna* (2013) with the Substance.

3.2. Assessment of the information provided

3.2.1. The provided study does not meet the specifications of the test guideline(s)

50 To fulfil the information requirement, a study must comply with the OECD TG 211 [and the specification(s) of OECD GD 23 if the substance is difficult to test] (Article 13(3) of REACH). Therefore, the following specification(s) must be met:

Technical specifications impacting the sensitivity/reliability of the test

a) the test medium fulfils the following condition: total organic carbon (TOC) ≤ 2 mg/L,;
b) the pH variation is < 1.5 units in one test;
c) the feed ration level is between 0.1 and 0.2 mg C/*Daphnia*/day;

Characterisation of exposure

d) analytical monitoring must be conducted. A reliable analytical method for the quantification of the test material in the test solutions with reported specificity, recovery efficiency, precision, limits of determination (i.e. detection and quantification) and working range must be available;

Reporting of the methodology and results

e) detailed information on feeding, including amount (in mgC/daphnia/day) and schedule is reported;
f) the nominal test concentrations and the results of all analyses to determine the concentration of the test substance in the test vessels are reported;
g) the full record of the daily production of living offspring during the test by each parent animal is provided;
h) the number of deaths among the parent animals and the day on which they occurred is reported;
i) the coefficient of variation for control reproductive output is reported;

51 In study (i)*:*

Technical specifications impacting the sensitivity/reliability of the test

a) total organic carbon (TOC) in the test medium is not reported;
b) the pH variation was by 1.7 units;
c) the feeding rate was not reported;

Characterisation of exposure

d) analytical monitoring of exposure was conducted; however the concentration of the test item was determined using a calibration curve based on the results of TOC measurements. The calibration curve of TOC measurement did not entirely

include the range of the tested concentrations (ie, not the lowest tested concentrations) and the Limit of Quantification reported in the dossier is higher than the NOEC identified in the study report. In the study summary it is reported "Only in the highest test concentration of nominal 20 mg test item/L a significant amount of carbon was found. Since the composition and therefore the carbon content of the test item is not available, only the measured content of carbon can be reported. In the test media of nominal 20 mg test item/L 3.4 mg carbon were found. As no nominal values for the carbon content are available all reported results refer to nominal test item concentration";

Reporting of the methodology and results

e) information on feeding rate is not provided;
f) the nominal test concentrations and the results of analyses to determine the concentration of the test substance in the test vessels are reported only for the highest tested concentration;
g) the full record of the daily production of living offspring during the test by each parent animal is not provided;
h) the number of deaths among the parent animals and the day on which they occurred is not reported;
i) the coefficient of variation for control reproductive output is not reported;

52 Based on the above,

- there are critical methodological deficiencies resulting in the rejection of the study results. More specifically, the reliability of the analytical method for the quantification of the substance in the test solutions is not established: the Limit of Quantification of the analytical method, higher than the proposed NOEC value, does not allow to verify the correct exposure of the tested organisms. Since the calibration curve of TOC measurement does not include all the tested concentrations, the exposure of the tested organisms to the Substance in the lowest tested levels is not demonstrated. You have not demonstrated that the measurement of TOC in the test and the reliance on an analytical method with a Limit of Quantification higher than the proposed NOEC value are a reliable method to quantify the Substance. Moreover, the feeding of the tested organisms could have an impact to the amount of organic carbon in the test medium and therefore to the analytical measurements, based on the TOC, resulting in a possible underestimation of aquatic toxicity.
- the reporting of the study is not sufficient to conduct an independent assessment of its reliability. The lack of statistical analysis on the results does not allow to verify the proposed NOEC. More specificallyyou have not demonstrated that the difference in parent survival between the control and the tested concentration proposed as NOEC is not statistically or biologically significant.

53 On this basis, the specification(s) of OECD TG 211 are not met.

54 Therefore, the information requirement is not fulfilled.

3.3. Study design

55 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 request 1.3.

56 In your comments on the initial draft decision you agree to conduct the study.

4. Long-term toxicity testing on fish

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

4.1. Information provided

58 You have adapted this information requirement by using Column 2 of Annex IX, Section 9.1. To support the adaptation, you have provided following information:

(i) "According to column 2 of Regulation (EC) No 1907/2006 Annex IX, section9.1.6, long-term toxicity testing shall be proposed if the chemical safety assessment indicates the need to investigate further the effects on aquatic organisms. A long-term test for aquatic invertebrates for the test substance is available. Based on short-term results the fish is not expected to be more sensitive than aquatic invertebrates. The endpoints for the three relevant aquatic trophic levels are in the same order of magnitude. As the bioaccumulation potential is low, and there is no indication that fishes are more sensitive than invertebrates, no long-term test with fish is proposed due to animal welfare as considered in Annex IX, section 9.1.6, column 2. In order to evaluate the long-term toxicity for aquatic organisms of Sulfonic acids, C14-16 (even numbered)-alkane hydroxy and C14-16 (even numbered)-alkene, sodium salts the experimental results for aquatic invertebrates and algae are considered".

4.2. Assessment of the information provided

4.2.1. Annex IX, Section 9.1., Column 2 is not a valid basis to omit the study

59 Under Annex IX, Section 9.1., Column 2 is not a basis for omitting information on long-term toxicity to fish referred to under Column 1, Section 9.1.6.

60 Your adaptation is therefore rejected.

61 Therefore, the information requirement is not fulfilled.

4.3. Study design

62 To fulfil the information requirement for the Substance, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (Guidance on IRs and CSA, Section 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 request 1.3.

63 In your comments on the initial draft decision you indicate that you will consider the possibility for adaptations before conducting a new study.

5. Extended one-generation reproductive toxicity study

64 An extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is an information requirement under Annex X, Section 8.7.3. Furthermore Column 2 defines the conditions under which the study design needs to be expanded.

5.1. Information provided

65 You have adapted this information requirement by referring to the availability of a pre-natal developmental toxicity study.

66 You have also adapted this information requirement by referring to Annex IX, Section 8.7.3, Column 1, using a carcinogenicity study.

5.2. Assessment of the information provided

67 A registrant may only adapt this information requirement based on the general rules set out in Annex XI or the specific rules set out in Annex X, Section 8.7., column 2.

68 A pre-natal developmental toxicity study or the legal provision of Annex IX, Section 8.7.3., column 1 that you refer to are not adaptation possibilities for waiving an experimental study at Annex X.

69 Your justification to omit this information does not refer to any legal ground for adaptation under Annex XI to REACH or Annex X, Section 8.7., Column 2 and, in the case of the first adaptation, the legal basis you are relying on for your intended adaptation is not apparent to ECHA.

70 Therefore, you have not demonstrated that this information can be omitted.

5.3. Study design

5.3.1. Species and route selection

71 As the Substance is a solid, the study must be conducted with oral administration of the Substance (Annex X, Section 8.7.3, Column 1).

5.3.2. Pre-mating exposure duration

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

73 Ten weeks pre-mating 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 (Guidance on IRs and CSA, Section R.7.6.).

74 Therefore, the requested pre-mating exposure duration is ten weeks.

5.3.3. Dose-level setting

75 The aim of the requested test must be to demonstrate whether the classification criteria of the most severe hazard category for sexual function and fertility (Repr. 1B; H360F) and developmental toxicity (Repr. 1B; H360D) under the CLP Regulation apply for the Substance (OECD TG 443, paragraph 22; OECD GD 151, paragraph 28; introductory part of Annex IX/X to REACH; Annex I, Section 1.0.1. to REACH and Recital 7, Regulation 2015/282), and whether the Substance meets the criteria for a Substance of very high concern regarding endocrine disruption according to Art.57(f) of REACH as well as supporting the identification of appropriate risk management measures in the chemical safety assessment.

76 To investigate the properties of the Substance for these purposes, the highest dose level must be set on the basis of clear evidence of an adverse effect on sexual function and fertility, but no deaths (i.e., no more than 10% mortality; Annex I, Section 3.7.2.4.4. of the CLP Regulation) or severe suffering such as persistent pain and distress (OECD GD 19, paragraph 18) in the P0 animals.

77 In case there are no clear evidence of an adverse effect on sexual function and fertility, the limit dose of at least 1000 mg/kg bw/day or the highest possible dose level not causing severe suffering or deaths in P0 must be used as the highest dose level. A descending

sequence of dose levels should be selected to demonstrate any dose-related effect and aiming to establish the lowest dose level as a NOAEL.

78 In summary: unless limited by the physical/chemical nature of the Substance, the highest dose level in P0 animals must be as follows:

(1) in case of clear evidence of an adverse effect on sexual function and fertility without severe suffering or deaths in P0 animals, the highest dose level in P0 animals must be determined based on such clear evidence, or

(2) in the absence of such clear evidence, the highest dose level in P0 animals must be set to be the highest possible dose not causing severe suffering or death, or

(3) if there is such clear evidence but the highest dose level set on that basis would cause severe suffering or death, the highest dose level in P0 animals must be set to be the highest possible dose not causing severe suffering or death, or

(4) the highest dose level in P0 animals must follow the limit dose concept.

79 You have to provide a justification with your study results demonstrating that the dose level selection meets the conditions described above.

80 Numerical results (i.e. incidences and magnitudes) and description of the severity of effects at all dose levels from the dose range-finding study/ies must be reported to facilitate the assessment of the dose level section and interpretation of the results of the main study.

5.3.4. Cohorts 1A and 1B

81 Cohorts 1A and 1B belong to the basic study design and must be included.

5.3.4.1. Histopathological investigations in Cohorts 1A and 1B

82 In addition to histopathological investigations of cohorts 1A, organs and tissues of Cohort 1B animals processed to block stage, including those of identified target organs, must be subjected to histopathological investigations (according to OECD TG 443, paragraph 67 and 72) if

- the results from Cohort 1A are equivocal,
- the test substance is a suspected reproductive toxicant or
- the test substance is a suspected endocrine toxicant.

5.3.4.2. Splenic lymphocyte subpopulation analysis

83 Splenic lymphocyte subpopulation analysis must be conducted in Cohort 1A (OECD TG 443, paragraph 66; OECD GD 151, Annex Table 1.3).

5.3.4.3. Investigations of sexual maturation

84 To improve the ability to detect rare or low-incidence effects, all F1 animals must be maintained until sexual maturation to ensure that sufficient animals (3/sex/litter/dose) are available for evaluation of balano-preputial separation or vaginal patency (OECD GD 151, paragraph 12 in conjunction with OECD TG 443, paragraph 47). For statistical analyses, data on sexual maturation from all evaluated animals/sex/dose must be combined to maximise the statistical power of the study.

5.3.5. Further expansion of the study design

85 The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if relevant information becomes available from other studies or during conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Annex X, Section 8.7.3., Column 2. 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 Guidance on IRs & CSA, Section R.7.6.

86 In your comments on the initial draft decision you indicate that you will consider the possibility for adaptations before conducting a new study.

References

The following documents may have been cited in the decision.

Guidance on information requirements and chemical safety assessment (Guidance on IRs & CSA)

Chapter R.4 Evaluation of available information; ECHA (2011).
Chapter R.6 QSARs, read-across and grouping; ECHA (2008).
Appendix to Chapter R.6 for nanoforms; ECHA (2019).
Chapter R.7a Endpoint specific guidance, Sections R.7.1 – R.7.7; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Chapter R.7b Endpoint specific guidance, Sections R.7.8 – R.7.9; ECHA (2017).
Appendix to Chapter R.7b for nanomaterials; ECHA (2017).
Chapter R.7c Endpoint specific guidance, Sections R.7.10 – R.7.13; ECHA (2017).
Appendix to Chapter R.7a for nanomaterials; ECHA (2017).
Appendix R.7.13-2 Environmental risk assessment for metals and metal compounds; ECHA (2008).
Chapter R.11 PBT/vPvB assessment; ECHA (2017).
Chapter R.16 Environmental exposure assessment; ECHA (2016).

Guidance on data-sharing; ECHA (2017).
Guidance for monomers and polymers; ECHA (2012).
Guidance on intermediates; ECHA (2010).
All guidance documents are available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

RAAF, 2017 Read-across assessment framework (RAAF); ECHA (2017).
RAAF UVCB, 2017 Read-across assessment framework (RAAF) – considerations on multi- constituent substances and UVCBs; ECHA (2017).

The RAAF and related documents are available online:
https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

***OECD Guidance documents* (OECD GDs)**

OECD GD 23 Guidance document on aquatic toxicity testing of difficult substances and mixtures; No. 23 in the OECD series on testing and assessment, OECD (2019).
OECD GD 29 Guidance document on transformation/dissolution of metals and metal compounds in aqueous media; No. 29 in the OECD series on testing and assessment, OECD (2002).
OECD GD 150 Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption; No. 150 in the OECD series on testing and assessment, OECD (2018).
OECD GD 151 Guidance document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test; No. 151 in the OECD series on testing and assessment, OECD (2013).

Appendix 2: 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 03 August 2022.

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).

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

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 3: Addressee(s) of this decision and their corresponding information requirements

In accordance with Articles 10(a) and 12(1) of REACH, the information requirements for individual registrations are defined as follows:

- the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Where applicable, the name of a third-party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.

Appendix 4: Conducting and reporting new tests for REACH purposes

1. Requirements when conducting and reporting new tests for REACH purposes

1.1. 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[2].

(4) Under the introductory part of Annexes VII/VIII/IX/X to REACH, where a test method offers flexibility in the study design, for example in relation to the choice of dose levels or concentrations, the chosen study design must ensure that the data generated are adequate for hazard identification and risk assessment.

1.2. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

(1) Selection of the Test material(s)
The Test Material used to generate the new data must be selected taking into account the following:

- the variation in compositions reported by all members of the joint submission,
- the boundary composition(s) of the Substance,
- the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

(2) Information on the Test Material needed in the updated dossier

- You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
- The reported composition must include the careful identification and description of the characteristics of the Tests Materials in accordance with OECD GLP (ENV/MC/CHEM(98)16) and EU Test Methods Regulation (EU) 440/2008 (Note,

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

Annex), namely all the constituents must be identified as far as possible as well as their concentration. Also any constituents that have harmonised classification and labelling according to the CLP Regulation must be identified and quantified using the appropriate analytical methods,

With that detailed information, ECHA can confirm whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers (https://echa.europa.eu/manuals).