~~Confidential~~

Helsinki, 26 October 2022

Addressees
Registrant(s) of 68425-15-0_JS as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
18/02/2022

Registered substance subject to this decision ("the Substance")
Substance name: Polysulfides, di-tert-dodecyl
EC number: 270-335-7

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

DECISION ON TESTING PROPOSAL(S)

Based on Article 40 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below by **3 November 2025** from the date of the decision.

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

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

1. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: EU B.56./OECD TG 443) by oral route, in rats, specified as follows:
   - 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 effects 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) with extension to mate Cohort 1B animals to produce the F2 generation which shall be followed to weaning; and
   - Cohort 3 (Developmental immunotoxicity).

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

The reasons for the decision(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 decision
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 decision

Contents

Reasons for the decision(s) related to the information under Annex X of REACH

1. Extended one-generation reproductive toxicity study

1 The basic test design of an extended one-generation reproductive toxicity study (EOGRTS) is a standard information requirement under Annex X to the REACH Regulation. Furthermore, column 2 of Section 8.7.3. defines when the study design needs to be expanded.

1.1. Information provided to fulfil the information requirement

2 You have submitted a testing proposal for an EOGRTS according to OECD TG 443 with the Substance.

3 ECHA requested your considerations for alternative methods to fulfil the information requirement for Toxicity to reproduction. You provided your considerations concluding that there were no alternative methods which could be used to adapt the information requirement(s) for which testing is proposed. ECHA has taken these considerations into account.

4 ECHA agrees that an EOGRTS is necessary.

1.2. Specification of the study design

1.2.1. Species and route selection

5 You proposed testing in the rat by oral route. ECHA agrees with your proposal.

1.2.2. Pre-mating exposure duration

6 You did not specify the pre-mating exposure duration.

7 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 pre-mating exposure duration (Guidance on IRs & CSA, Appendix R.7.6-3).

8 In addition, the substance is lipophilic (log Kow > 4.5); therefore, ten weeks pre-mating is required to ensure that a steady state is reached in the parental animals before mating.

1.2.3. Dose-level setting

9 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, para. 22; OECD GD 151, para. 28; Annex I Section 1.0.1. of 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.

10 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; Section 3.7.2.4.4 of Annex I to the CLP Regulation) or severe suffering such as persistent pain and distress (OECD GD 19,

para. 18) in the P0 animals.

11 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.

12 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.

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

14 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.

1.2.4. Cohorts 1A and 1B

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

16 Splenic lymphocyte subpopulation analysis

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

18 Investigations of sexual maturation

19 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, para. 12 in conjunction with OECD TG 443, para. 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.

1.2.5. Extension of Cohort 1B

20 If the Column 2 conditions of 8.7.3. are met, Cohort 1B must be extended by mating the Cohort 1B animals to produce the F2 generation.

21 The extension is required, among others, if the use of the Substance is leading to significant exposure of consumers and professionals (column 2, first para., point (a) of Section 8.7.3.) and if there are indications that the internal dose for the Substance will reach a steady state in the test animals only after an extended exposure (column 2, first paragraph, point (b), second indent of Section 8.7.3.).

22 The use of the Substance is leading to significant exposure of professionals because the Substance is used by professionals as an additive in lubricants and greases (PROCs 1, 2, 8a, 8b, 10, 11, 13, 15, 17, 20).

23 Furthermore, there are indications that the internal dose for the Substance and/or any of its metabolites will reach a steady state in the test animals only after an extended exposure. Specifically, the logKow for the Substance is above 4.5 (IUCLID Section 4.7) indicating potential accumulation.

24 You have proposed not to include an extension of Cohort 1B.

25 But for the reasons stated above, ECHA considers that Cohort 1B must be extended.

26 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, para. 67 and 72) because there is a concern for reproductive toxicity/endocrine activity indicated by the toxicity-triggers to extend the Cohort 1B.

27 The F2 generation must be followed to weaning allowing assessment of nursing and lactation of the F1 parents and postnatal development of F2 offspring. Investigations for F2 pups must be similar to those requested for F1 pups in OECD TG 443 and described in OECD GD 151.

1.2.6. Cohort 3

28 The developmental immunotoxicity Cohort 3 needs to be conducted in case of a particular concern on (developmental) immunotoxicity.

29 Existing information on the Substance itself derived from the available *in vivo* study (OECD TG 408, 2021) shows evidence of immunomodulation. Following treatment, the relative spleen weight was increased in the high dose male animals with statistical significance (numerical data not provided). Concerning blood parameters, a trend towards a higher mean white blood cell count in both sexes and a trend towards an increase in the neutrophil counts in both sexes were reported (males in all dose groups up to 87% and females in mid and high dose groups up to 24%; not statistically significant). As the immune system is sensitive to other toxicities which were noted following treatment, secondary effects to other toxicity could not be excluded at this time point.

30 However, following six weeks of recovery, statistically significant change was noted in the spleen weight of the male animals (numerical data not provided in the dossier) and statistically significant increase in the neutrophil counts were noted in both sexes (males +118% and females +69%). Following the recovery period no other toxicity was noted, therefore secondary effects to other toxicity can be excluded. Therefore, the changes observed after recovery reflect a direct immunotoxicological effect of the Substance, and not an effect secondary to other toxicity.

31 The ECHA Guidance R.7a, p. 531 further specifies that the DIT cohort could be triggered based on existing information on the substance itself derived from relevant available *in vivo* studies when there is a "[c]ombination of at least two (statistically significant and) biologically meaningful changes in haematology/clinical chemistry and/or organ weight associated with immunotoxicity, e.g. reduced leucocyte count in combination with reduced spleen weight". Since there are effects both on spleen weight and neutrophil number in the study, this shows a concern for (developmental) immunotoxicity for the Substance.

32 For the reasons stated above, the developmental immunotoxicity Cohort 3 must be conducted.

33 In your comments, you disagree with the inclusion of Cohort 3. You query the relevance and sensibility of the information requirement for the DIT cohort based on a general concern on the implementation and validation of the DIT arm in EOGRTS. Your comments do not address the concern for (developmental) immunotoxicity for the Substance and you have not provided a valid reason why the conditions for including cohort 3 would not apply to your Substance. Furthermore, ECHA notes that OECD TG 443 underwent extensive

validation, and includes provisions to ensure that the conduct of the study yields meaningful results. A test laboratory should always follow the test guideline, and be proficient to carry out the investigations it offers.

1.3. Outcome

34 Under Article 40(3)(b) your testing proposal is accepted under modified conditions, and you are requested to conduct the test with the Substance, as specified above.

1.3.1. Further expansion of the study design

35 No triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) were identified. However, you may expand the study by including Cohorts 2A and 2B 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 Column 2, Section 8.7.3., Annex X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in Guidance on IRs & CSA, Section R.7.6.

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).

All Guidance on REACH is 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

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 18 February 2021.

ECHA held a third party consultation for the testing proposal(s) from 18 March 2021 until 3 May 2021. ECHA did not receive information from third parties.

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

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

ECHA did not receive any comments within the commenting period.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

ECHA received proposal(s) for amendment and did not modify the draft decision.

ECHA invited you to comment on the proposed amendment(s) and referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

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 modified the draft decision prior to the Member State Committee meeting discussion. The Member State Committee unanimously agreed on the draft decision during its MSC-79 meeting. ECHA adopted the decision under Article 51(6) of REACH.

Appendix 3: Addressees 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 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]

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

1. *Selection of the Test material(s)*

The Test Material used to generate the new data must be selected taking into account the following:

a) the boundary composition(s) of the Substance,

b) 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*

a) 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.

b) 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, 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.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[3].

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