

Helsinki, 14 January 2022

**Addressees**

Registrants of JS\_Reactive\_Red\_141 listed in the last Appendix of this decision

**Date of submission of the dossier subject of a decision**

04/10/2018

**Registered substance subject to this decision, hereafter 'the Substance'**

Substance name: Octasodium 2,2'-[1,4-phenylenebis[imino(6-chloro-1,3,5-triazine-4,2-diyl)imino(1-hydroxy-3,6-disulphonatonaphthalene-2,8-diyl)azo]]bisnaphthalene-1,5-disulphonate

EC number: 275-108-6

CAS number: 71002-20-5

**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 **22 July 2024**.

The requested information must be generated using the Substance unless otherwise specified.

**A. Information required from the Registrants subject to Annex VIII of REACH**

**1. Extended one-generation reproductive toxicity study (Annex VIII, Section 8.7.3. and Section 0.5. of Annex I of REACH; test method: OECD TG 443) in rats, oral (gavage) route specified as follows:**

- **At least two weeks pre-mating exposure duration for the parental (P0) generation;**
- **Dose level setting shall aim to induce systemic toxicity at the highest dose level;**
- **Cohort 1A (Reproductive toxicity);**
- **Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation which shall be followed to weaning.**

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

Reasons for the request are explained in the following appendix entitled "Reasons to request information required under Annexes VIII of REACH".

**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 and VIII to REACH, for registration at 10-100 tpa.

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 testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil 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 can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: <http://echa.europa.eu/regulations/appeals>.

Approved<sup>1</sup> under the authority of Mike Rasenberg, Director of Hazard Assessment

---

<sup>1</sup> As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

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

This decision is based on the examination of the testing proposals you submitted and on scientific information submitted by third parties.

### 1. Extended one-generation reproductive toxicity study

According to Annex VIII, 8.7.1., Column 2, at the tonnage level of 10 to 100 tonnes per annum, the Registrant may propose an extended one-generation reproductive toxicity study (EOGRTS, OECD TG 443) (Annex IX, section 8.7.3) or a pre-natal developmental toxicity study (PNDT, OECD TG 414) (Annex IX, Section 8.7.2) instead of a screening study (OECD TG 421/422) in cases where there are serious concerns about the potential for adverse effects on fertility or development.

Pursuant to Article 12(1) and Annex VI of the REACH Regulation the standard information requirements listed in Annex VII to X of the REACH Regulation are considered minimum requirements. Annex VI, step 4 of the 'Guidance note on fulfilling the requirements of Annexes VI to XI' provides that the rules set out in Annexes VII to XI may require certain tests to be undertaken earlier than or in addition to the standard requirements. Furthermore, in accordance with Annex I of the REACH Regulation, certain additional information may have to be generated if it is necessary for producing the chemical safety report (CSR). According to the last subparagraph of Section 0.5. of Annex I of REACH, if the manufacturer or importer considers that further information is necessary for producing his CSR and that this information can only be obtained by performing tests in accordance with Annex IX and X, he shall submit a proposal for a testing strategy, explaining why he considers that additional information is necessary and record this in the CSR under the appropriate heading. Further, under Section 1.3.2 of Annex I to REACH, if the information is inadequate to decide whether a substance should be classified for a particular hazard class or category, the registrant shall indicate and justify the action or decision he has taken as a result.

This means that when justified, higher tier/further studies may be conducted for substances where the tonnage level would not normally require this as a standard requirement. In order to understand the toxicological properties of the Substance in light of the adverse effects observed, it is necessary to investigate further so that appropriate risk management measures can be put in place and safe use of the substance can be ensured.

Your dossier contains a combined repeated dose toxicity study with the reproduction / developmental toxicity screening test (██████████ 2018; OECD TG 422) with the Substance. In this study, *"The reduction in the number of uterine implantations at 330 mg/kg/day (and as a consequence litter size) was associated with the slightly low post implantation survival index. This effect, however, was statistically significant and all parameters were outside of the Historical Control Data values (representing 11 OECD TG 422 studies). This effect is considered to be potentially related to treatment and it is assumed likely that the male and/or female reproductive systems have been affected, but the mechanism is undetermined and potentially adverse."* The high dose group had excess mortality (3/10 males and 1/10 females) and the dosing of 1000 mg/kg bw/day was ceased and remaining animals were terminated early.

In addition, the study demonstrated a statistically significant shift in gestation length in 330 mg/kg bw/day dose group (2/10 females 23.5 day, 1/10 female 25 day) in comparison with control group (23 day). The result was also above Historical control data (HCD). Also in the 330 mg/kg bw/day dose group, one female had a total litter loss at gestation day (GD) 25 and indication of an inactive mammary gland based on macroscopic examination.

You have not self-classified your Substance for Reproductive toxicity and despite of the identified serious concern, you state that no final conclusion can be drawn on the reduced uterine implantations and litter size seen in the mid dose group in the presence of severe maternal and paternal toxicity observed in the high dose group in the combined screening study. To clarify the concern and toxicity profile of the Substance, you propose an EOGRTS to finally decide on the potential classification for toxicity to fertility.

The adverse effects on reproduction (reduction in the number of uterine implantations, reduced litter size, low post implantation survival index, increased gestation length and one total litter loss at GD 25) reported in the combined screening test (OECD TG 422) at dose level 330 mg/kg bw/day without excess mortality and severe toxicity are significant in number and severity and raise serious concerns. These toxicological properties need to be further investigated in order to conclude on risk assessment and classification based on a more definitive study design and thus in order to produce the CSR. This is necessary for appropriate risk management measures.

#### 1.1 Information provided to fulfil the information requirement

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

ECHA requested your considerations for alternative methods to fulfil the information requirement for Reproductive toxicity. 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.

ECHA received third party information concerning the testing proposal during the third party consultation. For the reasons explained further below the information provided by third parties is not sufficient to fulfil this information requirement.

*A third party has indicated that: "A screening study (OECD 422) is available for the registered substance, which is a data requirement at this tonnage band indicated in the registration dossier (10-100 tpa). The Registrant states that 'no final conclusion can be drawn on the reduced uterine implantations and litter size in the presence of severe maternal and paternal toxicity observed in the Combined Repeated Dose Toxicity Study and Reproductive /Developmental Toxicity Screening Study. A final EOGRTS is proposed to finally decide on potential classification for toxicity to fertility.' If the tonnage band is 10-100 tpa (as indicated in the registration dossier), an EOGRTS is not required. Annex VIII (8.7.1) states that the EOGRTS may be proposed instead of performing the screening study, but does not state that an EOGRTS is triggered by the results of a screening study. At a tonnage band of 100-1000 tpa, an EOGRTS may be proposed by a Registrant where screening studies indicate 'adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity' (Annex IX, 8.7.3). For this particular substance, relevant effects (decreased implantations and litter size) were seen in the screening study at the mid-dose level of 330 mg/kg bw/d were noted to be associated with 'severe toxicity' (the high dose group administered 1000 mg/kg bw/d having been terminated early). No relevant effects were seen at 100 mg/kg bw/d. Given the clear association between reproductive effects and 'severe toxicity', it is questionable whether an EOGRTS is required under Annex IX data requirements."*

As noted above, the available information does not support the conclusion in this comment and the toxicological properties of the Substance need to be further investigated to conclude on risk assessment and classification based on a more definitive study design and careful dose level selection, in order to produce the CSR.

An EOGRS is appropriate to investigate the adverse effects described above.

Therefore, ECHA agrees that an EOGRS is necessary to address the identified concerns in relation with reproductive toxicity.

For the reasons discussed above, ECHA notes that there is a serious concern about the potential for adverse effects on reproduction, especially on sexual function and fertility and a need to investigate further.

ECHA considers that an EOGRS (OECD TG 443) is necessary to address the identified concerns in relation with reproductive toxicity as it is a suitable study to cover effects on parturition and peri- post-natal pup development as it strongly seems that the concern relates to these life stages. It is essential to be able to assess the hazard and evaluate the risk of observed primary effects (delayed parturition and dystocia) in a study with high statistical power and exposure duration covering the critical period of delivery.

In addition to confirming and further investigating effects on sexual function and fertility and peri- post-natal developmental toxicity, EOGRS may show more effects related to the (potentially hormonal) modes of action because more sensitive parameters are investigated with higher statistical power than the screening study. This will lead to more reliable NOAEL values and more reliable hazard classification.

### *1.2 Specification of the study design*

#### *Species and route selection*

You proposed testing in the rat. ECHA agrees with your proposal because the rat is the species preferred by OECD TG 443. You shall aim to conduct the study using the same rat strain that was used for the OECD TG 422 study.

You proposed testing by oral (dietary) route in rats. ECHA considers that the oral route is the most appropriate route of administration, however you shall use gavage dosing to replicate the administration route of the OECD TG 422.

#### *Pre-mating exposure duration and dose-level setting*

You proposed 10 weeks pre-mating exposure duration. A minimum of 2-week pre-mating exposure duration for P0 animals is required because the full spectrum of parameters on sexual function and fertility will be covered in the F1 animals (ECHA Guidance R.7a, Appendix R.7.6-3).

In order to be compliant and not to be rejected due to too low dose levels, the highest dose level must aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects, with the other cohorts being tested at the same dose levels. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

If there is no existing relevant data to be used for dose level setting, it is recommended that results from a range-finding study (or range-finding studies) are reported with the main study.

You must provide a justification with your study report that demonstrate that the dose level selection meets the conditions described above.

### *Cohorts 1A and 1B*

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

### *Extension of Cohort 1B*

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.

The extension is required, among others, if the use of the Substance is leading to significant exposure of consumers and professionals (column 2, first paragraph, point (a) of Section 8.7.3.) and if there are indications of one or more relevant modes of action related to endocrine disruption from available *in vivo* studies or non-animal approaches (column 2, first paragraph, point (b), third indent of Section 8.7.3.).

The use of the Substance reported in the joint submission is leading to significant exposure of consumers and professionals because the Substance is used by professionals as water based inks and laboratory use (PROCs 8a, 8b, 9, 10, 15, 28) and consumers as water based inks (cartridges, pens) and the Substance is used in plastic and paper articles.

Furthermore, there are indications of one or more modes of action related to endocrine disruption because changes in organs/parameters sensitive to endocrine activity are observed in the combined screening test (OECD TG 422). In particular, changes in gestation length, changes in organ weights of slightly lower body weight adjusted epididymides and testes weights in males receiving 330 mg/kg/day and group mean adjusted ovary and uterus, cervix and oviducts weights were slightly low for females given 100 or 330 mg/kg/day.

You did not propose to include an extension of Cohort 1B.

ECHA concludes that an extension of Cohort 1B is necessary.

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. It is recommended to aim at 20 litters per dose group.

### *1.3 Outcome*

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

### *Further expansion of the study design*

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 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 Column 2, Section 8.7.3., Annex IX/X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance R.7a, Section R.7.6.

## **Appendix B: 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<sup>2</sup>.

### **B. 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 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 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<sup>3</sup>.

---

<sup>2</sup> <https://echa.europa.eu/practical-guides>

<sup>3</sup> <https://echa.europa.eu/manuals>

**Appendix C: Procedure**

ECHA started the testing proposal evaluation in accordance with Article 40(1) on 5 October 2020.

ECHA held a third party consultation for the testing proposal(s) from 16 December 2020 until 1 February 2021. ECHA received information from third parties (see Appendix A, section 1.1.).

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 took into account your comments and amended the deadline.

In your comments on the draft decision, you requested an extension of the deadline to provide information from 24 to 36 months from the date of adoption of the decision. To support your request, you provided preliminary schedules from CROs regarding foreseen timelines to perform OECD TG 443.

ECHA acknowledges the information provided and understands that an extension is required.

On this basis, ECHA has granted the request and extended the deadline to 30 months.

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 D: List of references - ECHA Guidance<sup>4</sup> 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)<sup>5</sup>

RAAF - considerations on multi-constituent substances and UVCBs (RAAF UVCB, March 2017)<sup>6</sup>

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.

---

<sup>4</sup> <https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment>

<sup>5</sup> <https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across>

<sup>6</sup> [https://echa.europa.eu/documents/10162/13630/raaf\\_uvcb\\_report\\_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316](https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316)

OECD Guidance documents<sup>7</sup>

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

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.

---

<sup>7</sup> <http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm>

**Appendix E: 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.

<b>Registrant Name</b>	<b>Registration number</b>	<b>Highest REACH Annex applicable to you</b>
[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.