~~Confidential~~

Helsinki, 11 January 2023

Addressees
Registrant(s) of Reactive Blue 203 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
20/11/2015

Registered substance subject to this decision ("the Substance")
Substance name: Tetrasodium 4-amino-6-[[2,5-dimethoxy-4-[[2-(sulphonatooxy)-ethyl]sulphonyl]phenyl]azo]-5-hydroxy-3-[[4-[[2-(sulphonatooxy)ethyl]sulphonyl]-phenyl]azo]naphthalene-2,7-disulphonate
EC number: 282-468-8

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 the deadline of ***20 January 2025***.

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

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

1. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490)

2. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) by oral route, in rats

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

0. Reasons common to several requests 4

Reasons related to the information under Annex VIII of REACH 7

1. In vitro gene mutation study in mammalian cells 7

2. Screening for reproductive/developmental toxicity 7

References 9

0. Reasons common to several requests

0.1. Assessment of the read-across approach

1 You have adapted the following standard information requirements by using grouping and read-across approach under Annex XI, Section 1.5:

i. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

ii. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

2 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 sections.

3 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.

4 Additional information on what is necessary when justifying a read-across approach can be found in the Guidance on IRs and CSA, Chapter R.6. and related documents (RAAF, 2017; RAAF UVCB, 2017).

0.1.1. Predictions for toxicological properties

5 You provide a read-across justification document in IUCLID Section 13.

6 You predict the properties of the Substance from information obtained from the following source substance(s):

i. Reactive Black 5, tetrasodium 4-amino-5-hydroxy-3,6-bis[[4-[[2-(sulphonatooxy)ethyl] sulpho-nyl]phenyl]azo]naphthalene-2,7-disulpho-nate (CAS 17095-24-8, EC 241-164-5)

ii. Reactive Red 198, 5-[[4-chloro-6-[(3-sulphophenyl)amino]-1,3,5-triazin-2-yl]amino]-4-hydroxy-3-[[4-[[2-(sulphooxy)ethyl]sulphonyl]phenyl]azo]naphthalene-2,7-disulphonic acid, sodium salt (CAS 78952-61-1, EC 279-015-1)

7 You provide the following reasoning for the prediction of toxicological properties: ”Given that the metabolism of dyestuffs is understood and due to the similarities in the physico-chemical properties between the molecules, and the common “skeleton” and cleavage products of the structure, it is considered a viable conclusion to state that the expected (eco)toxicological effects for Reactive Blue 203 and the structural analogues selected are likely to be similar.”

8 ECHA understands that your read-across hypothesis is based on the formation of common (bio)transformation products. You predict the properties of your Substance to be quantitatively equal to those of the source substance.

9 We have identified the following issue(s) with the prediction(s) of toxicological properties:

0.1.1.1. Missing supporting information

10 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 supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

11 As indicated above, your read-across hypothesis is based on the (bio)transformation of the Substance and of the source substance(s) to a common compound(s). In this context, exposure to the Substance and of the source substance(s) may also lead to exposure to other compounds than the common compound of interest. The impact of exposure to these non-common compounds on the prediction of properties of the target needs to be assessed to ensure that a reliable prediction can be made.

12 You have provided experimental information with Reactive Black 5 and Reactive Red 198 assumed to produce only unmethoxylated benzene (bio)transformation product(s) whereas the Substance is assumed to produce also dimethoxylated benzene (bio)transformation product(s) according to your read-across justification document.

13 In your comments to the draft decision you are referring to the OECD TG 474 mammalian erythrocyte micronucleus study with [redacted] (EC [redacted]), that is included in your dossier, as supporting information for your read-across hypothesis. ECHA acknowledges that [redacted] is assumed to produce dimethoxylated (bio)transformation product(s) based on your read-across hypothesis. The OECD TG 474 study is however related to cytogenicity whereas the information requirements covered by your read-across approach are related to gene mutation and reproductive toxicity. You did not specify or provide experimental data with [redacted], or with other dimethoxylated source substances that would be assumed to produce dimethoxylated (bio)transformation product(s) based on your read-across hypothesis, and related to the adapted information requirements.

14 You attached OECD QSAR Toolbox alert profiles and bioavailability predictions for transformation products, target and source substances in your comments to the draft decision. You state that it is not considered necessary to conduct additional studies with Reactive Blue 203 "based on this additional information given on the dimethoxylated transformation product and the additional data that will be added to the Read-Across Justification."

15 ECHA notes that there are structural differences between the target and source substances, and their degradation products. While the similarity in presence or absence of structural alerts may indicate that the differences do not influence the reactivity of the substance e.g. on the protein or DNA, this information does not confirm, on its own, that the Substance and the source substances have similar toxicological properties. In fact, the complexity of the systemic interactions and the large number of targets/mechanisms associated with those broad areas of toxicity (e.g. reproductive toxicity) is not covered by computational tools. Therefore, the structural alerts and bioavailability predictions reported in your comments do not qualify as supporting information on the above mentioned properties of the Substance and the source substances, such as e.g. supporting information that would include studies of comparable design and duration.

16 In the absence of experimental information on source substance(s) producing dimethoxylated (bio)transformation products, you have not provided sufficient supporting information to scientifically justify your read-across hypothesis and the read-across

predictions, because you did not assess the impact of exposure to these non-common compounds on the prediction of properties of the target.

0.1.2. Conclusion on the read-across approach

17 For the reasons above, you have not established that relevant properties of the Substance can be predicted from data on the source substance(s). Your read-across approach under Annex XI, Section 1.5. is rejected.

Reasons related to the information under Annex VIII of REACH

1. 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.

1.1. 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.

1.2. Information provided

21 You have adapted this information requirement by using a Grouping of substances and read-across approach and provided the following information:

i. An *in vitro* mammalian cell gene mutation study (2014) with source substance Reactive Red 198

1.3. Assessment of the information provided

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

1.3.1. Read-across adaptation rejected

23 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected.

1.4. Specification of the study design

24 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.

2. Screening for reproductive/developmental toxicity

25 A screening for reproductive/developmental toxicity study (OECD 421 or OECD 422) is an information requirement under Annex VIII, Section 8.7.1., if there is no evidence from analogue substances, QSAR or in vitro methods that the substance may be a developmental toxicant.

2.1. Information provided

26 You have adapted this information requirement by using Column 2 of Annex VIII, Section 8.6.1. To support the adaptation, you have provided following information:

i. Justification: "*A developmental/teratogenicity study without adverse effects is*

available for a structural analogue, and is offered in Section 7.8.2. Hence, a reproductive/developmental screening study has not to be performed according to Column 2 of REACH Annex VIII. Furthermore, no effects were seen on reproductive organs in the repeat dose study and the category of substance (reactive dyes) is not known for reproductive toxicity effects. On the basis of animal welfare it is proposed that the developmental/teratogenicity study in conjunction with the lack of effects noted in the other toxicity studies is suitable to address this endpoint"

ii. A prenatal developmental toxicity study (1994) with the source substance Reactive Black 5

2.2. Assessment of the information provided

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

2.2.1. The available study is not reliable

28 Under Annex VIII, Section 8.7., Column 2, the study does not need to be conducted if a pre-natal developmental toxicity study (OECD TG 414) is already available.

29 The study ii. is described as a prenatal developmental toxicity study.

30 However, for the reasons explained in Section 2.2.2 the study is not reliable.

31 Therefore, your adaptation is rejected.

2.2.2. Read-across adaptation rejected

32 As explained in Section 0.1., your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5. is rejected.

2.3. Specification of the study design

33 A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats.

34 The study must be conducted with oral administration of the Substance (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

35 Therefore, the study must be conducted in rats with oral administration of the Substance.

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

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 15 November 2021.

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: 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 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;

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:

- 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[3].

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