

Helsinki, 16 March 2020

Addressee

Registrant of JS_406-860-7 listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision

23/02/2015

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

Substance name: 7-((E)-(2-((aminocarbonyl)amino)-4-((4-chloro-6-((2-((2-hydroxyalkyl)oxy)alkyl)amino)-1,3,5-triazin-2-yl)amino)phenyl)diazenyl) polycarbocyclo, polysulfonate, sodium salt

EC number: 406-860-7

CAS number: NS

Decision number: [Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/D)]**DECISION ON A COMPLIANCE CHECK**Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of **23 March 2021**.**A. Requirements applicable to all the Registrants subject to Annex VII of REACH**

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

B. Requirements applicable to all the Registrants subject to Annex VIII of REACH

1. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method OECD 421/422) in rats, oral route with the Substance;

Conditions to comply with the requests

You are bound by the requests for information set out in this decision.

The Appendices A and B state the reasons for the requests for information to fulfil the requirements set out in the respective Annexes of REACH.

The Appendix entitled Observations and technical guidance addresses the generic approach for the selection and reporting of the test material used to perform the required studies and provides generic recommendations and references to ECHA guidance and other reference documents.

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

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>.

Approved¹ under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

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

Appendix A: Reasons for the requests to comply with Annex VII of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier registered at 1 to 10 tonnes or more per year must contain, as a minimum, the information specified in Annex VII to REACH.

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

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

You have provided a key study in your dossier:

- i. An *in vitro* gene mutation study according to EU-Method B 13/14 with the following *Salmonella typhimurium* strains, TA 1535, TA 1537, TA 1538, TA 98, and TA 100 with and without metabolic activation (████, 1990).

We have assessed this information and identified the following issue:

To fulfil the information requirement, the study has to meet the requirements of OECD TG 471 (1997)². The key parameters of this test guideline include:

- a) If the Substance is an azo-dye or a diazo-compound, the test in presence of metabolic activation must be performed following the Prival modification.
- b) TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101)

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

- a) the Prival modification, in spite of the fact that the tested substance is an azo-dye.
- b) the appropriate 5 strains, as the information provided does not include results in the required fifth strain, *S. typhimurium* TA 102 or *E. coli* WP2 uvrA or *E. coli* or *E. coli* WP2 uvrA (pKM101).

Therefore, the information provided does not cover a key parameter required by OECD TG 471 and the information requirement is not fulfilled.

In your comments on the draft decision you agreed to perform the requested test.

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

Appendix B: Reasons for the requests to comply with Annex VIII of REACH

Under Articles 10(a) and 12(1) of REACH, a technical dossier registered at 10 to 100 tonnes or more per year must contain, as a minimum, the information specified in Annexes VII and VIII to REACH.

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

Screening for reproductive/developmental toxicity is a standard information requirement in Annex VIII to REACH.

You have provided a key study in your dossier, study performed with an analogue substance (EC [REDACTED]):

- i. [REDACTED] 2013, according to OECD TG 421 (1995) with a NOAEL for fertility and developmental toxicity at the highest dose of 1000 mg/kg bw/d.

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. You have provided a read-across justification document in IUCLID Section 13.

You read-across between the structurally similar substances, [REDACTED] as source substance and the Substance as target substance.

You have provided the following reasoning for the prediction of toxicological properties: "...based on chemical similarity, comparable properties are expected..." for the Substance and a source substance. You state that the fluoro-triazenyl structure present in the Substance is "...much more reactive (worst case)..." than the chloro-triazenyl reactive group present in the source substance. You state that "In case of reductive cleavage during metabolism all formed amines..." from the Substance are also present with the source. You identify that a structural difference between substances (vinyl sulfonyl group) may contribute to the skin sensitisation potential observed with the Substance and not with the source substance. You identify that two other chlorotriazenyl dyes do not show findings on the endpoint needed for read across.

ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted based on a worst-case approach.

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

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

of prediction(s)'). Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance³ and related documents^{4, 5}.

More specifically, Annex XI, Section 1.5 of the REACH Regulation states that "*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*". For this purpose "*it is important to provide supporting information to strengthen the rationale for the read-across*"⁶. The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s).

Supporting information must include information to confirm your claimed worst-case prediction.

1.1. Missing supporting information to substantiate worst-case consideration

As indicated above, your read-across hypothesis is based on the assumption that the source substance constitutes a worst-case for the prediction of the property under consideration of the Substance. In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substance(s) is necessary to confirm a conservative prediction of the properties of the Substance from the data on the source substance(s). Such information can be obtained, for example, from bridging studies of comparable design and duration for the Substance and of the source substance.

As part of your read across hypothesis you aim to fulfill the information requirement for the screening for reproductive/developmental toxicity test (OECD Test Guideline 421 or OECD 422). According to these Test Guidelines the test can be used to provide initial information on possible effects on reproduction and/or development. The Guidelines set out a number of requirements such as, for example, a need for dosing of the Substance for a minimum of four weeks for males and of sufficient duration for females to cover pre-mating, conception, pregnancy and lactation and the examination of parameters for sexual function and fertility such as those for mating and fertility/duration of gestation, parturition, and lactation.

Firstly, you have provided a screening for reproductive/developmental toxicity study (OECD 421, with GLP) conducted in the rat for the source substance. The animals were dosed for up to 54 days covering, for example, pre-mating, conception, pregnancy and lactation. Males were exposed for 28 days. You report a NOAEL for foetal toxicity of 1000 mg/kg.

As supporting information, you consider that the substances show similar properties because comparable results were observed in short-term repeated dose toxicity (28 day) studies conducted in rat for the Substance and the source substance. In these studies you report that no toxicologically significant effects were observed up to the top dose of 1000 mg/kg bw/day. The test on the Substance showed that treatment of male rats at 1000 mg/kg/day (top dose)

³ Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals. 2008 (May) ECHA, Helsinki. 134. pp. Available online: https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf/77f49f81-b76d-40ab-8513-4f3a533b6ac9

⁴ Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: [Read-Across Assessment Framework \(https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across\)](https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)

⁵ Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: <https://doi.org/10.2823/794394>

⁶ Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

for 4 weeks was associated with treatment-related colouration of the urine in the absence of other toxicologically significant findings and is not considered an adverse effect. The results of these tests support your claim that the absence of a treatment-related effect with the source substance is "in line" with the results reported for the Substance.

However, ECHA considers that these 28 day studies do not address all the parameters that should be addressed according to the OECD 421 or 422 Test Guideline. Females were exposed for 28 days and not the period necessary to cover pre-mating, conception, pregnancy and lactation, therefore these studies do not provide the necessary information on sexual function and fertility such as information on mating and fertility/duration of gestation, parturition, and lactation of the animals. Therefore, there is no basis to draw comparison between the substances for such additional parameters. It therefore cannot be established that a conservative prediction is possible for the properties under consideration.

Secondly, as supporting information, ECHA notes that you include in your "Justification of the analogue approach" document information about two other chlorotriazenyl dye substances with reproductive/developmental toxicity screening studies which you report to show findings comparable with those available for the Substance and the source substance. These data are not present in the technical dossier of the Substance. Additionally, there are structural differences between the two chlorotriazenyl dyes and they also differ from the Substance and the source substance e.g. degree of sulphonation among others. However, you have not addressed the impacts of these structural differences on your read across hypothesis. Therefore, it cannot be assessed if the information supports your hypothesis.

In your comments on the draft decision you re-iterated the arguments for the read-across already discussed above.

In addition you provided a Jaccard or Tanimoto similarity index and a further narrative of chemical similarity of target & source substances. ECHA understands that these QSAR predictions are provided as a weight of evidence information to support the low toxicity claim. However, while they provide supporting information, these data cannot mitigate the deficiencies highlighted above for the read-across.

You also pointed out that "*The number of azo-bonds does not differ as stated in the comments from ECHA*". ECHA has corrected the draft decision by removing reference to different number of azo-bonds.

You proposed to update the dossier with further information on the reproductive and developmental toxicity of two additional chloro-triazenyl dyes (██████████). The results of these studies may strengthen the read-across and further support the claim of low toxicity providing that the structural differences and their impact on the basis for predicting the toxicity is explained. However, ECHA notes that at the moment there is no justification provided in the dossier for using the results of these two substances to support the adaptation.

The data set reported in the technical dossier does not include relevant, reliable and adequate information for the Substance and the source substance(s) to support your read-across hypothesis in respect of the property under consideration.

In the absence of such information, you have not established that the source substance constitutes a worst-case for the prediction of the property under consideration of the Substance. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

1.2. Missing information on the impact of common and non-common compounds

As indicated above, you also consider that your read-across hypothesis is supported due to (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.

You state that, in case of reductive cleavage of the azo bonds during metabolism, all formed amines from the Substance are also present in the source substance. You further state that there is difference in reactivity between the Substance and the source due to the presence of a vinyl sulfone group.

You have not provided information characterising the exposure to the common or the non-common compounds resulting from exposure to the Substance and of the source substance(s). No experimental data or other adequate and reliable information addressing the impact of exposure to the common and non-common compounds is included in the documentation of your read-across approach in respect of the property under consideration.

In your comments on the draft decision you re-iterated the claim that "*In case of reductive cleavage of the azo bonds of the dyes during metabolism all formed amines from [REDACTED] [REDACTED] are also present in the tested substance [REDACTED].*". However, ECHA notes that this claim still needs to be justified to verify the read-across hypothesis.

In the absence of such information, you have not established that a reliable prediction of the property under consideration of the Substance can be derived on the basis of your read-across hypothesis. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

Conclusions on the read-across approach

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

Therefore, the information requirement is not fulfilled.

Information on study design

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 with oral⁷ administration of the Substance.

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

Appendix C: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of registration dossiers after the date on which you were notified the draft decision according to Article 50(1) of REACH.

The compliance check was initiated on 7 March 2019.

ECHA notified you of the draft decision and invited you to provide comments within 30 days of the notification.

ECHA took into account your comments and did not amend the requests.

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: Observations and technical guidance

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

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of the Member States.

3. Test guidelines, GLP requirements and reporting

Under Article 13(3) of REACH, all new data generated as a result of this decision needs to be conducted according to the test methods laid down in a European Commission Regulation or according to international test methods recognised by the Commission or ECHA as being appropriate.

Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses shall be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

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: 'How to report robust study summaries'⁸.

4. Test material

Selection of the test material(s)

The registrants of the Substance are responsible for agreeing on the composition of the test material to be selected for carrying out the tests required by the present decision. The test material selected must be relevant for all the registrants of the Substance, i.e. it takes into account the variation in compositions reported by all members of the joint submission. The composition of the test material(s) must fall within the boundary composition(s) of the Substance.

While selecting the test material you must take into account 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.

Technical reporting of the test material

The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers"⁹.

⁸ <https://echa.europa.eu/practical-guides>

⁹ <https://echa.europa.eu/manuals>

5. List of references of the ECHA Guidance and other guidance/ reference documents¹⁰

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 in this decision.

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 in this decision.

ECHA Read-across assessment framework (RAAF, March 2017)¹¹

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.

OECD Guidance documents¹²

Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD23.

Guidance Document on Mammalian Reproductive Toxicity Testing and Assessment – No 43, referred to as OECD GD43.

¹⁰ <https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment>

¹¹ <https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across>

¹² <http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm>

Appendix E: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fulfilled

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.