~~Confidential~~

Helsinki, 17 November 2022

Addressees
Registrants of JS_CAS_157577-99-6 as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
14/06/2021

Registered substance subject to this decision ("the Substance")
Substance name: Disodium; 4-Amino-3-{4-[4-(2,4-diamino-phenylazo)-benzenesulfonylamino]-phenylazo}-5-hydroxy-6-phenylazo-naphthalene-2,7-disulfonate
EC/List number: 605-104-5

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 ***26 May 2026***.

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 cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.; test method: OECD TG 473) or In vitro micronucleus study (Annex VIII, Section 8.4.2.; test method: OECD TG 487)

2. Justification for an adaptation of a Short-term repeated dose toxicity (28 days) based on the results of the Sub-chronic toxicity study (90 days) requested below (Annex VIII, Section 8.6.1.)

3. Simulation testing on ultimate degradation in surface water also requested below (triggered by Annex VIII, Section 9.2.)

4. Identification of degradation products also requested below (triggered by Annex VIII, Section 9.2.)

5. Bioaccumulation in aquatic species also requested below (triggered by Annex I, Sections 0.6.1. and 4; Annex XIII, Section 2.1.)

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

6. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.; test method: OECD TG 408) by oral route, in rats

7. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat or rabbit)
8. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: EU C.47./OECD TG 210)

9. Simulation testing on ultimate degradation in surface water (Annex IX, Section 9.2.1.2.; test method: EU C.25./OECD TG 309) at a temperature of 12°C. Non-extractable residues (NER) must be quantified and a scientific justification of the selected extraction procedures and solvents must be provided.

10. Identification of degradation products (Annex IX, 9.2.3.; test method: EU C.25./OECD TG 309)

11. Bioaccumulation in aquatic species (Annex IX, Section 9.3.2; test method: EU C.13./OECD TG 305)

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.

In the requests above, the same study has been requested under different Annexes. This is because some information requirements may be triggered at lower tonnage band(s). In such cases, only the reasons why the information requirement is triggered are provided for the lower tonnage band(s). For the highest tonnage band, the reasons why the standard information requirement is not met and the specification of the study design are provided. Only one study is to be conducted; all registrants concerned must make every effort to reach an agreement as to who is to carry out the study on behalf of the others under Article 53 of REACH.

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. In addition, the studies relating to biodegradation and bioaccumulation are necessary for the PBT assessment. However, to determine the testing needed to reach the conclusion on the persistency and bioaccumulation of the Substance you should consider the sequence in which these tests are performed and other conditions described in this Appendix.

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

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0. Reasons common to several requests

0.1. Grouping and read-across adaptation

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

- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

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. Assessment of read-across approach

0.1.1.1. 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 substances:

SS01 Acid Black 210, EC No. 421-880-6 (Na salt)
SS02 Acid Black 210, EC No. 286-384-2 (K salt)

7 You provide the following reasoning for the prediction of toxicological properties: "*The read across strategy will be mostly based on toxicokinetics* (TK) assessment of the target and analogue substances. The substances undergo if not the same, a similar metabolic pathway and therefore the toxicity potency of the analogue substances (and consequently the tests results) can be applied also to the target substance". You explain that Acid Black 234 and Acid Black 210 are practically identical except for a nitro group missing on Acid Black 234. For Acid black 234, you acknowledge a possible release of aniline instead of p-nitroaniline in source substances.

8 ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effects. 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:

0.1.1.1.1. Read-across hypothesis contradicted by existing data

10 Annex XI, Section 1.5. provides that "substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances". The Guidance on IRs and CSA, Section R.6.2.2.1.f. indicates that "it is important to provide supporting information to strengthen the rationale for the read-across". The set of supporting information must 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 selected source substances.

11 The observation of differences in the toxicological properties between the source substances and the Substance would contradict the hypothesis that the properties of the Substance can be predicted from the data on the source substances. An explanation why such differences do not affect the read-across hypothesis must be provided and supported by scientific evidence.

12 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar Substance and source substances cause the same type of effects. However, your assumption is challenged by the following facts:

- As indicated in your justification for the read-across, the cleavage of the azo bond may generate aromatic amines that may be absorbed. Following the reduction of azo bond, the target substance may produce aniline and the source substance p-nitroaniline. Aniline is subject to harmonized classification for Skin sens. 1, STOT RE 1, Muta 2 and Carc. 2. According to the information notified on p-nitroaniline, this substance is not sensitising, not mutagenic and with different potency following repeated dose exposure (STOT RE 2)[2]. Therefore, the substance and the source substance lead to the formation of (bio)transformation products with different type of effects.

13 Moreover, your assumption on the the same type of effects is challenged by the following facts:

- You argue on very low absorption and systemic availability as well as minimal azo-reduction events. However, the systemic effects reported, for example after repeated dose exposure, are clear indications of absorption. Given the physico-chemical properties of the target and source and their high molecular weights (860.8 g/mol for the Substance and 905.8 and 938.0 g/mol, respectively, for the Na and K salts of the source substance), the effects observed may rather be due to the resulting metabolites.
- You argue that testing with Acid Black 210 is a more conservative approach and that "*at the intermediate dose 450 and 150 mg/kg/d, minor effects are seen* [with the Substance] *in comparison with Acid Black 210*". However, ECHA notes that in the dose range finding study to an OECD 422 with the Substance, all males and females died during the first week of the study at the dose level 1000 mg/kg/day. But, in an OECD 407, the same dose level of Acid Black 210 induced no treatment-related mortality. In the OECD 422 study with source substance Acid Black 210, 12 animals/sex/dose were used in an exposure regimen of 54-56 days. The data available for the Substance are from a dose range finding study done with 6 animals/sex/dose with 42 days exposure for males and 40 days exposure for females. Therefore, at similar exposure duration, observing more severe effects following exposure to the Substance cannot be excluded.
- Available information indicate that the effects seen following exposure to the the Substance are more similar to the ones appearing after aniline administration. In particular you report the following: "*histopathological examination of spleen in males at the dose levels 150 and 450 mg/kg/day and in females at the dose level*

[2] https://echa.europa.eu/information-on-chemicals/cl-inventory-database/-/discli/details/99504

450 mg/kg/day revealed siderosis, extramedullary hemopoiesis and venostasis". Perturbation of iron metabolism, siderosis and increased extramedullary haematopoiesis was also reported in studies with anilin (MAK for Aniline, DOI: 10.1002/3527600418.mb6253e6419). Vascular congestion of the spleen was also reported as one the most sensitive early changes for aniline toxicity in addition to Hb adduct formation (Mellert *et al.* 2004, doi: 10.1191/0960327104ht466oa). This supports a possible contribution of aniline, as a reduction product, to the toxicity seen with the target substance.

- An analogue substance, Acid Black 1 which may also lead to aniline formation, was reported in Colipa Opinion B 15 (referred by you in the read-across justification) as causing changes in haematological parameters and histological findings in the spleen in a 90d study even at the lowest dose of 4.7 mg active dye/kg bw/day. This suggests difference of effects between the dyes that may release aniline and dyes releasing other metabolites, at least for repeated dose toxicity.

14 In you dossier you state that "[t]he available data from animal studies did not give evidence for a specific embryotoxic, fetotoxic or teratogenic potential of aniline. Therefore, the presence of aniline is not considered to have an impact on the behaviour of ABK234". Neither aniline nor p-nitraniline are reported to show reproductive toxicity. Therefore, for this endpoint, the formation of aniline is not considered to have a significant impact on the prediction. Consequently, your read-across hypothesis for this endpoint is supported.

15 The available information on the possible metabolites from the Substance and source substances indicate differences in their toxicological properties. This contradicts your read-across hypothesis whereby the Substance and source substances cause the same type of effects. Therefore, you have not demonstrated and justified that, for genetic toxicity and repeated dose toxicity, the properties of the source substances and of the Substance are likely to be similar despite the observation of these differences.

0.1.1. Conclusion on the read-across approach

16 For the reasons above, you have not established that relevant properties (i.e., genetic toxicity and repeated dose toxicity) 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 for these enpoints.

Reasons related to the information under Annex VIII of REACH

1. In vitro cytogenicity study in mammalian cells or In vitro micronucleus study

17 An in vitro cytogenicity study in mammalian cells or an in vitro micro-nucleus study is an information requirement under Annex VIII to REACH (Section 8.4.2.).

1.1. Information provided

(i) a study according to OECD 487 (2010) with the source substance Acid Black 210 (Na salt; EC 421-880-6);

(ii) a study according to OECD 474 (1996) with the source substance Acid Black 210 (Na salt) EC 421-880-6).

1.2. Assessment of the information provided

1.2.1. Invalid read-across adaptation

18 The studies (i.) and (ii.) above were performed with the source substance Acid Black 210 (Na salt). However, 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. In addition, ECHA identified the endpoint-specific issue addressed below.

1.2.2. Study not conducted according to the applicable test guideline

19 To fulfil the information requirement the study has to be an in vitro chromosomal aberration test or an in vitro micronucleus test, conducted in mammalian cells in accordance with OECD TG 473 or OECD TG 487, respectively (Guidance on IRs and CSA, Table R.7.7–2). These test guidelines impose the following specifications:

a) Two separate test conditions must be assessed: in absence of metabolic activation and in presence of metabolic activation.
b) The maximum concentration tested must induce 55+5% of cytotoxicity compared to the negative control, or the precipitation of the tested substance.
c) At least 3 concentrations (not including the solvent and positive controls) that meet the acceptability criteria (appropriate cytotoxicity, number of cells, etc) should be evaluated.
d) At least 2000 cells must be scored per concentration.
e) Data on the cytotoxicity and the frequency of micronuclei for the treated and control cultures must be reported.

20 However, in relation to the above specifications, the reporting of study (i) shows that:

a) The test was only conducted in the absence of metabolic activation.
b) No viable cells have been scored at the two highest concentrations used on V79 cells.
c) Since the first two concentrations were too toxic, the results were obtained only at two concentrations: 0.1 and 0.032 mg/ml.
d) In the study it is reported that "*At least 1000 cells were evaluated for each plate*".
e) Data on the cytotoxicity and/or the frequency of micronuclei for the treated and control cultures are not reported for all the concentrations.

21 The information provided does not cover key parameters required by OECD TG 487.

22 Therefore, the information requirement is not fulfilled.

23 In the comments to the draft decision, you agree to perform the requested study.

1.3. Study design and test specifications

24 To fulfil the information requirement for the Substance, either in vitro cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2., test method OECD TG 473) or in vitro micronucleus study (Annex VIII, Section 8.4.2., test method OECD TG 487) are considered suitable.

2. Justification for an adaptation of a Short-term repeated dose toxicity (28 days) based on the results of the Sub-chronic toxicity study (90 days)

25 A short-term repeated dose toxicity study (28 days) is an information requirement under Annex VIII to REACH (Section 8.6.1.). This information may take the form of a study record or a valid adaptation in accordance with either a specific adaptation rule under Column 2 of Annex VIII to REACH or a general adaptation rule under Annex XI to REACH.

2.1. Information provided

(i) a dose range finding study for a study according to OECD 422 (2021) with the Substance;
(ii) a study according to OECD 407 (1996) with the source substance Acid Black 210 (Na salt; EC 421-880-6);
(iii) a study according to OECD 422 (2011) with the source substance Acid Black 210 (Na salt; EC 421-880-6).

2.2. Assessment of the information provided

2.2.1. Invalid read-across adaptation

26 The studies (ii.) and (iii.) were performed with the source substance Acid Black 210 (Na salt). However, 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. In addition, ECHA identified endpoint-specific issue(s) addressed below.

2.2.2. Study (i.) not conducted according to the applicable test guideline

To be considered compliant and enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL), a study has to meet the requirements of OECD TG 407. The following key parameter(s) of this test guideline include:

- examination of clinical biochemistry
- examination of the animals for organs weight and histopathology (including thyroid gland/ thyroid hormone measurements)

27 The study (i.) is a dose range finding study for an OECD 422 and, in relation to the above specifications, the reporting of this study shows that:

- clinical biochemistry was not examined,
- the animals were not examined for organs weight (except the gravid uterus) and histopathology, including thyroid gland/ thyroid hormone measurements (except for testicles and spleen in males and spleen in females).

28 Therefore, the information provided does not cover key parameters required by OECD TG 407.

29 Based on the above, the information you provided does not fulfil the information requirement.

30 Column 2 of Annex VIII, Section 8.6.1. provides that an experimental study for this endpoint is not needed if a reliable sub-chronic (90 days) or chronic toxicity study is available.

31 The present decision requests the registrants concerned to generate and submit a reliable sub-chronic toxicity study (90 days). According to Column 2 of Annex VIII, Section 8.6.1., and to prevent unnecessary animal testing, a short term toxicity study (28 days) does not therefore need to be conducted.

32 Because you still must comply with the information requirement in Annex VIII, Section 8.6.1., you are requested to submit a justification for the adaptation provided in Column 2 of that provision.

3. Simulation testing on ultimate degradation in surface water

33 Further degradation testing must be considered if the chemical safety assessment (CSA) according to Annex I indicates the need to investigate further the degradation of the substance (Annex VIII, Section 9.2., Column 2).

3.1. Triggering of further degradation testing

34 This information requirement is triggered in case the chemical safety assessment (CSA) indicates the need for further degradation investigation (Annex I, Section 4; Annex XIII, Section 2.1), such as if the substance is a potential PBT/vPvB substance (Guidance on IRs and CSA, Section R.11.4.). This is the case if the Substance itself or any of its constituent or impurity present in concentration ≥ 0.1% (w/w) or relevant transformation/degradation product meets the following criteria:

- it is potentially persistent or very persistent (P/vP) as it is not readily biodegradable (i.e. <60/70% degradation in an OECD 301);
- it is potentially bioaccumulative or very bioaccumulative (B/vB) as for some groups of substances (e.g. organometals, ionisable substances, surfactants) other partitioning mechanisms may drive bioaccumulation (e.g. binding to protein/cell membranes) and high potential for bioaccumulation cannot be excluded solely based on its potential to partition to lipid;
- it meets the T criteria set in Annex XIII: NOEC or EC10 < 0.01 mg/L or classification as carc. 1A or 1B, muta. 1A or 1B, repro. 1A, 1B or 2, or STOT RE 1 or 2.

35 Your registration dossier provides the following:

- The Substance is not readily biodegradable (QSAR estimation with QSAR dyes RC 2.0 model and based on Expert Judgement). Further, the Substance is not inherently biodegradable (38 % degradation after 28 days in OECD TG 302B by analogy to the analogue substance Acid Black 210 (K salt) with EC 286-384-2);
- The Substance is ionisable substance and therefore high potential for bioaccumulation cannot be excluded based on available information;

36 Furthermore,

- for the reasons explained in request 11 of this decision, it is not possible to conclude on the bioaccumulation potential of the Substance, and
- for the reasons explained in requests 1 and 6 to 8 of this decision, it is not possible to conclude on the toxicity of the Substance.

37 Under section 2.3 of your IUCLID dossier ('PBT assessment'), you conclude that the Substance is P but not B. In support of your conclusion you provide the following justification: "*The substance is not biodegradable and not hydrolysable, but it is very soluble with Kow of -3.1, therefore no bioaccumulation is foreseen. Furthermore a quick photolitic degradation both in water and in the air has to be considered*".

38 However, your claim that Log Kow is appropriate to determine whether the Substance is a potential B is incorrect for the following reason:

- For some groups of substances (e.g. organometals, ionisable substances, surfactants) other partitioning mechanisms may drive bioaccumulation (e.g. binding to protein/cell membranes). For this reason log Kow is not considered a valid descriptor of the bioaccumulation potential for such substances (Guidance on IRs and CSA, Appendix R.7.10-3).

39 Therefore, the additional information from your PBT assessment is not adequate to conclude that the Substance is not a potential PBT/vPvB substance.

40 Based on the above, the available information on the Substance indicates that it is a potential PBT/vPvB substance. Further, the additional information from your PBT assessment is not adequate to conclude on the PBT/vPvB properties of the Substance.

3.2. Information provided on further degradation

41 Your dossier contains no information on further degradation.

42 Therefore, the requirements for further degradation are not met and the information requirement is not fulfilled.

43 The examination of the available information or adaptations, your comments to the draft decision, as well as the selection of the requested test and the test design are addressed respectively under request 9.

4. Identification of degradation products

44 Further degradation testing must be considered if the chemical safety assessment (CSA) according to Annex I indicates the need to investigate further the degradation of the substance (Annex VIII, Section 9.2., Column 2).

45 This information requirement is triggered in case the chemical safety assessment (CSA) indicates the need for further degradation investigation (Annex I, Section 4; Annex XIII, Section 2.1), such as if the substance is a potential PBT/vPvB substance (Guidance on IRs and CSA, Section R.11.4.).

46 As already explained under request 3 the Substance is a potential PBT/vPvB substance.

47 Therefore, the chemical safety assessment (CSA) indicates the need for further degradation investigation.

48 The examination of the available information or adaptations, your comments to the draft decision, as well as further information on the selection of the approach to generate this information are addressed under request 10.

5. Bioaccumulation in aquatic species

49 Bioaccumulation in aquatic species is required for the purpose of PBT/vPvB assessment (Annex I, Sections 0.6.1 and 4 to REACH).

50 This information requirement is triggered in case the chemical safety assessment (CSA) indicates the need for further investigation on bioaccumulation in aquatic species (Annex I, Section 4; Annex XIII, Section 2.1), such as if the substance is a potential PBT/vPvB substance (Guidance on IRs and CSA, Section R.11.4.).

51 As already explained under request 3 the Substance is a potential PBT/vPvB substance.

52 Therefore, the chemical safety assessment (CSA) indicates the need for further investigation on bioaccumulation in aquatic species.

53 The examination of the available information or adaptations, your comments to the draft decision, as well as the selection of the requested test and the test design are addressed under request 11.

Reasons related to the information under Annex IX of REACH

6. Sub-chronic toxicity study (90-day)

54 A sub-chronic repeated dose toxicity study (90 days) is an information requirement under Annex IX to REACH (Section 8.6.2.).

6.1. Information provided

(i) a dose range finding study for a study according to OECD 422 (2021) with the Substance;
(ii) a study according to OECD 407 (1996) with the source substance Acid Black 210 (Na salt; EC 421-880-6);
(iii) a study according to OECD 422 (2011) with the source substance Acid Black 210 (Na salt; EC 421-880-6).

6.2. Assessment of the information provided

6.2.1. Invalid read-across adaptation

55 The studies (ii.) and (iii.) above were performed with the source substance Acid Black 210 (Na salt). However, 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. In addition, ECHA identified endpoint-specific issue addressed below.

6.2.2. Studies not conducted according to the applicable test guideline

56 To fulfil the information requirement, the sub-chronic toxicity study (90 day) has to meet the requirements of OECD TG 408. Therefore, the following specifications must be met:

a. At least 10 male and 10 female animals for each test and control group are used.
b. Dosing of the Substance is performed daily for a minimum of 90 days.
c. Clinical signs are observed daily and functional observations (i.e. sensory activity, grip strength and motor activity assessments) are conducted on week 11 or after.
d. The oestrus cycle in females is assessed at necropsy.
e. Full histopathology as specified in paragraphs 47-49 of the test guideline is conducted.

57 In study (i.) to (iii.), the following specifications are not according to the requirements of OECD TG 408:

a. Only 5 or 6 males/females in each test and control group were used in studies (i.) and (ii.), respectively.
b. The exposure duration was 40/42, 28 and 42/56 days in studies (i.) to (iii.), respectively.
c. Data on functional observations: the nature, severity and duration are missing in studies (i.) and (ii.).
d. Data on oestrus cycle are missing in study (ii.).
e. Data on histopathology findings: the incidence and severity is reported in 5-6 animals as in studies (i.) to (iii.) and not in 10 animals per sex per group as specified by the test guideline.

58 Based on the above, the information you provided does not fulfil the information requirement.

59 In the comments to the draft decision, you agree to perform the requested study.

6.3. Study design and test specifications

60 Following the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity of the Substance; Guidance on IRs and CSA, Section R.7.5.6.3.2.

61 According to the OECD TG 408, the rat is the preferred species.

62 Therefore, the study must be performed in rats according to the OECD TG 408, in rats and with oral administration of the Substance.

7. Pre-natal developmental toxicity study in a second species

63 A pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is an information requirement under Annex IX to REACH (Section 8.7.2.).

7.1. Information provided

64 You have provided a statement, in Section 7.8.2 of your dossier, that "the study does not need to be conducted because relevant human exposure can be excluded as demonstrated in the relevant exposure assessment". ECHA understands that you intended to adapt this information requirement on the basis of Annex XI, Section 3.

65 You have also provided the following study:

(i) a study according to OECD 422 (2011) with the source substance Acid Black 210 (Na salt; EC 421-880-6).

7.2. Assessment of the information provided

7.2.1. Invalid read-across adaptation

66 The study (i.) above was performed with the source substance Acid Black 210 (Na salt). However, 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.

7.2.2. Exposure-based waiving not in line with the conditions specified in Annex XI, Section 3

67 As stated in Annex XI, Section 3, testing in accordance with Sections 8.6 and 8.7 of Annex VIII and in accordance with Annexes IX and X may be omitted based on the exposure scenario(s) developed in the CSR, by providing an adequate and scientifically-supported justification based on a thorough and rigorous exposure assessment in accordance with Section 5 of Annex I and by communicating the specific conditions of use through the supply chain. Any one of the following criteria 3.2.(a),(b) or (c) shall be met:

- Under 3.2 (a), the manufacturer or importer demontrates and documents that all of the following conditions are fulfilled,
  i. the results of the exposure assessment covering all relevant exposures throughout the life cycle of the substance demonstrate the absence of or no significant exposure in all scenarios of the manufacture and all identified uses as referred to in Annex VI section 3.5.;

  However, you did not provide adequate and reliable documentation demonstrating the “absence of or no significant exposure in all scenarios of the manufacture and all identified uses”. The registered substance is used as a dye in leather and textile applications. Several exposure scenarios for

formulation, industrial and professional uses (ES 2, 3, 6 and 7) demonstrate potential exposure for workers as shown by your chemical safety report (CSR).

ii. a suitable DNEL or a PNEC can be derived from results of available test data for the Substance taking full account of the increased uncertainty resulting from the omission of the information requirement, and that DNEL or PNEC is relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes[1];

However, the worker long-term systemic DNEL, which you derived in your CSR, is based on Repeated Dose 28-day Oral Toxicity Study in Rodents (OECD 407). ECHA underlines that such DNEL is not relevant nor appropriate both for the information requirement to be omitted and for risk assessment purposes. A Repeated Dose 28-day Oral Toxicity Study does not investigate effects on mating, fertility, pregnancy, the foetuses' sex and body weight/external, skeletal and soft tissue alterations (variations and malformations)/number of resorptions and or live foetuses/ measurement of anogenital distance in live rodent foetuses. For these reasons, a DNEL derived from a Repeated Dose 28-day Oral Toxicity Study is not appropriate to omit a PNDT study. A screening study is neither appropriate to omit a PNDT study for the purpose of subparagraph 3.2(a)(ii) as stated in its note (1)[3].

iii. the comparison of the derived DNEL or PNEC with the results of the exposure assessment shows that exposures are always well below the derived DNEL or PNEC.

Since the DNEL is considered not appropriate, it follows that the third criterion 3.2(a)(iii), i.e. that is must be demonstrated that exposure results are to be well below the derived DNEL, cannot be fulfilled.

68 Moreover, for substances satisfying the PBT and vPvB criteria of Annex XIII, PNEC and PECs cannot be derived with sufficient reliability to demonstrate that the ratio between PECs and the PNEC are always well below 1 (conditions (ii) and (iii) above). As already explained under Request 3, the information from your dossier currently does not allow excluding that the Substance may be PBT/vPvB. Therefore, 3.2 (a), is not applicable to potential PBT/vPvB substances.

- Under 3.2 (b), where the substance is not incorporated in an article the manufacturer or the importer demonstrates and documents for all relevant scenarios that throughout the life cycle strictly controlled conditions as set out in Art 18(4)(a) to (f) apply;

  As mentioned above, in several exposure scenarios, the conditions of use and estimated exposure levels for the combined routes do not demonstrate strictly controlled conditions (SCC) as per Annex XI, section 3.2(b) and therefore criterion 3.2(b) for exposure-based adaptation is not satisfied. In particular, condition (a) as set out in Article 18(4) does not appear to be fulfilled because it has not been

[3] For the purpose of subparagraph 3.2(a)(ii), without prejudice to column 2 of Section 8.7 of Annexes IX and X, a DNEL derived from a screening test for reproductive/developmental toxicity shall not be considered appropriate to omit a prenatal developmental toxicity study or a two-generation reproductive toxicity study. For the purpose of subparagraph 3.2(a)(ii), without prejudice to column 2 of section 8.6 of Annexes IX and X, a DNEL derived from a 28-day repeated dose toxicity study shall not be considered appropriate to omit a 90-day repeated dose toxicity study.

demonstrated that the substance is rigorously contained by technical means during its whole lifecycle.

- Under 3.2 (c), where the substance is incorporated in an article in which it is permanently embedded in a matrix or otherwise rigorously contained by technical means, it is demonstrated and documented that all of the following conditions i) to (iii) are fulfilled, where the first condition is
  i. the substance is not released during its life cycle.
  ii. the likelihood that workers or the general public or the environment are exposed to the substance under normal or reasonably foreseeable conditions of use is negligible; and
  iii. the substance is handled according to the conditions set out in Article 18(4)(a) to (f) during all manufacturing and production stages including the waste management of the substance during these stages.

The substance is incorporated in a textile and a leather articles (AC 5 and 6) as a dye. However, no releases during its life cycle, nor strictly controlled conditions as set out in Article 18(4)(a) to (f) are demonstrated in the provided CSR.

69 Therefore, based on the information you provided in the registration dossier, the general rules for adaptation of Annex XI, Section 3 are currently not fulfilled. Consequently, your adaptation is rejected.

7.2.3. Study not adequate for the information requirement

70 (Eco)toxicological studies must comply with a recognised test method (Art. 13(3) of REACH), in this case OECD TG 414. Such study must cover the key parameters of the corresponding OECD test guideline (Art. 13(3) of REACH). Therefore, the following specifications must be met:

a. 20 female animals with implantation sites for each test and control group are used;
b. The examination of the foetuses for external, skeletal and soft tissue alterations (variations and malformations) is conducted.

71 The study (i.) is described as "*reproduction/ developmental toxicity screening test*". This study has been conducted using the OECD TG 422 which is a screening tests rather than a conclusive developmental toxicity study. In any case, that study does not cover the key parameters of the OECD TG 414 such as:

a. A statistical power equivalent to the OECD TG 414, as the study provided includes only 12 animals in each dose group.
b. Skeletal and soft tissue alterations (variations and malformations) were not assessed.

72 The study is not adequate for the information requirement and is therefore rejected.

73 On this basis, the information requirement is not fulfilled.

74 In the comments to the draft decision, you agree to perform the requested study.

7.3. Study design and test specifications

75 A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species.

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

77 Therefore, the study must be conducted in rats or rabbits with oral administration of the Substance.

8. Long-term toxicity testing on fish

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

8.1. Information provided

79 In the registration dossier, you have provided a justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2. In support of your adaptation, you provided the following justification: "*the chemical safety assessment, according to Annex I, does not indicate the need to investigate further the effects on aquatic organisms*".

80 In the comments to the draft decision, you provided a justification to adapt this information requirement by using substance-tailored exposure-driven testing under Annex XI, Section 3.2 (a).

8.2. Assessment of the information provided in the registration dossier

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

81 Annex IX, Section 9.1., Column 2 does not allow omitting the need to submit information on long-term toxicity to fish under Column 1. It must be understood as a trigger for providing further information on long-term toxicity to fish if the chemical safety assessment according to Annex I indicates the need (Decision of the Board of Appeal in case A-011-2018).

82 Your adaptation is therefore rejected.

8.3. Assessment of the information provided in the comments to the draft decision

8.3.1. The exposure based adaptation under Annex XI, Section 3.2 (a) is not valid

83 As already explained under Request 9 below, Annex XI, Section 3.2 (a) is not applicable to potential PBT/vPvB substances.

84 Therefore, your adaptation is rejected.

85 On this basis, the information requirement is not fulfilled.

8.4. Study design and test specifications

86 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.).

9. Simulation testing on ultimate degradation in surface water

87 Simulation testing on ultimate degradation in surface water is an information requirement under Annex IX to REACH (Section 9.2.1.2.).

9.1. Information provided

88 An adaptation under Annex XI, Section 3 ('Substance-tailored exposure-driven testing'). In support of your adaptation, you provide the following statement: "*Based on REACH regulation, annex XI.3 Testing in accordance with Annex IX and Annex X may be omitted, based on the exposure scenario(s) developed in the Chemical Safety Report. Based on the description of uses and the attached exposure scenario, water is not exposed to the substance*".

9.2. Assessment of the information provided

9.2.1. Annex XI, Section 3 (a) is not applicable to potential PBT/vPvB substances

89 Under Annex XI, Section 3(a), this information may be omitted based on the exposure scenario(s) developed in the Chemical Safety Report. The justification must be based on a rigorous exposure assessment in accordance with Annex I, Section 5 and must meet any one of the following criteria:

i. the absence or no significant exposure in all scenarios of the manufacture and all identified uses referred to in Annex VI, Section 3.5.,
ii. a predicted no effect concentration (PNEC) can be derived from available data, which:
   - must be relevant and appropriate both to the information requirement to be omitted and for risk assessment purposes and therefore must be based on reliable information on the hazardous properties of the substance on at least three trophic levels;
   - must take into account the increased uncertainty resulting from the omission of the information requirement, in this case by selecting an appropriate assessment factor (AF) as described in ECHA Guidance R.10.3, and
iii. the ratio between the results of the exposure assessment (PECs) and the PNEC are always well below 1.

90 For substances satisfying the PBT and vPvB criteria of Annex XIII, long-term effects and the estimation of the long-term exposure cannot be carried out with sufficient reliability (Annex I, Section 4.0.1). As a result, for such substances PNEC and PECs cannot be derived with sufficient reliability to demonstrate that the ratio between PECs and the PNEC are always well below 1 (conditions (ii) and (iii) above). Consequently, such information cannot be used to demonstrate that no significant exposure occurs in all scenarios of the manufacture and all identified uses referred to in Annex VI, Section 3.5 (condition (i) above).

91 As already explained under request 3, the information from your dossier currently does not allow excluding that the Substance may be PBT/vPvB.

92 Therefore, you have not demonstrated that the ratio between the reported PECs and the currently available PNEC provide a reliable means to demonstrate the absence of significant exposure of the environment. As a result, the conditions set out under Annex XI, Section 3.2(a) are not met.

93 On this basis the information requirement is not fulfilled and your adaption is rejected.

9.2.2. The adaptations from Annex XI, Section 3.2 (b) or (c) are not justified

94 The required information may be omitted if the substance meet the conditions as specified in Annex XI, Section 3.2 (b) or (c) of Annex XI.

95 As already explained under request 7 the information you provided in the dossier does not meet the general rules for adaptation of Annex XI, Section 3.2 (b) and (c), as none of the criteria of that adaptation are currently fulfilled. The adaptation you provided is not in line with the conditions specified in Annex XI, Section 3.

96 Your adaptation is therefore rejected.

97 On this basis, the information requirement is not fulfilled.

98 In the comments to the draft decision, you state that "*the adaptation can be accepted if the PBT assessment will result in a lack of concern, according to the criteria of Annex XIII*" and that "*the substance is persistent, but not toxic and not bioaccumulative, therefore not considered either PBT or vPvB*". As explained under Request 11, it is not possible to conclude on the bioaccumulation potential of the Substance in aquatic species. Therefore, the information in your comments does not allow excluding that the Substance may be PBT/vPvB.

9.3. Study design and test specifications

99 Simulation degradation studies must include two types of investigations (Guidance on IRs and CSA, Section R.7.9.4.1.):

1) a degradation pathway study where transformation/degradation products are quantified and, if relevant, are identified, and
2) a kinetic study where the degradation rate constants (and degradation half-lives) of the parent substance and of relevant transformation/degradation products are experimentally determined.

100 You must perform the test, by following the pelagic test option with natural surface water containing approximately 15 mg dw/L of suspended solids (acceptable concentration between 10 and 20 mg dw/L) (Guidance on IRs and CSA, Section R.11.4.1.1.3.).

101 The required test temperature is 12°C, which corresponds to the average environmental temperature for the EU (Guidance on IRs and CSA, Table R.16-8) and is in line with the applicable test conditions of the OECD TG 309.

102 As specified in Guidance on IRs and CSA, Section R.7.9.4.1., the organic carbon (OC) concentration in surface water simulation tests is typically 2 to 3 orders of magnitude higher than the test material concentration and the formation of non-extractable residues (NERs) may be significant in surface water tests. Therefore, non-extractable residues (NER) must be quantified. The reporting of results must include a scientific justification of the used extraction procedures and solvents. By default, total NER is regarded as non-degraded Substance. However, if reasonably justified and analytically demonstrated a certain part of NER may be differentiated and quantified as irreversibly bound or as degraded to biogenic NER, such fractions could be regarded as removed when calculating the degradation half-life(s) (Guidance on IRs and CSA, Section R.11.4.1.1.3.). Further recommendations may be found in the background note on options to address non-extractable residues in regulatory persistence assessment available on the ECHA website.

103 Relevant transformation/degradation products are at least those detected at ≥ 10% of the applied dose at any sampling time or those that are continuously increasing during the study even if their concentrations do not exceed 10% of the applied dose, as this may indicate persistence (OECD TG 309; Guidance on IRs and CSA, Section R.11.4.1.).

10. Identification of degradation products

104 Identification of degradation products is an information requirement under Annex IX to REACH (Section 9.2.3.).

105 You have provided no information on the identity of transformation/degradation products for the Substance in the registration dossier.

106 In the comments to the draft decision, you have provided QSAR predictions of the identity of the potential degradation products with BIOWIN 4.10.

10.1. Assessment of information provided

107 To fulfil the information requirement, information on the identity of relevant transformation/degradation products must be provided (Annex XIII, fifth paragraph; Guidance on IRs and CSA, Section R.11.4.1.).

108 In the QSAR prediction provided in your comments, 6 potential transformation/degradation products were identified. However, you have not provided information on the stability, behaviour, and molar quantity of the degradation/transformation products relative to the Substance. Furthermore, in your comments to the draft decision, you state that "*the adaptation can be accepted if the PBT assessment will result in a lack of concern, according to the criteria of Annex XIII*" and that "*the substance is persistent, but not toxic and not bioaccumulative, therefore not considered either PBT or vPvB*". As explained under Request 11, it is not possible to conclude on the bioaccumulation potential of the Substance in aquatic species. Therefore, the information in your comments does not allow excluding that the Substance may be PBT/vPvB.

109 This information is required for the purpose of the PBT/vPvB assessment (Annex I, Section 4) and the risk assessment (Annex I, Section 6) of the Substance.

110 On this basis, the information requirement is not fulfilled.

10.2. Study design and test specifications

111 Identity, stability, behaviour, and molar quantity of the degradation/transformation products relative to the Substance must be evaluated and reported, when analytically possible. In addition, degradation half-life, log K_{ow} and potential toxicity of the transformation/degradation may need to be investigated. You must obtain this information from the degradation study requested under request 9.

112 To determine the degradation rate of the Substance, the requested study according to OECD TG 309 (Request 9) must be conducted at 12°C and at a test concentration < 100 µg/L. However, to overcome potential analytical limitations with the identification and quantification of major transformation/degradation products, you may consider running a parallel test at higher temperature (but within the frame provided by the test guideline, e.g. 20°C) and at higher application rate (i.e. > 100 µg/L).

11. Bioaccumulation in aquatic species

113 Bioaccumulation in aquatic species is an information requirement under Annex IX to REACH (Section 9.3.2.).

11.1. Information provided

114 In the registration dossier, you have provided an adaptation under Annex IX, Section 9.3.2., Column 2 with the following justification: "*the Substance has low potential for bioaccumulation*".

115 In the comments to the draft decision, you provide a justification to adapt this information requirement by applying weight of evidence (WoE) adaptation in accordance with Annex XI, section 1.2:

i. LogBCF values for analogue substances derived from studies performed under the Japanese Regulatory framework.

ii. Scientific publication entitled [redacted] (1981)
iii. Survey report, [redacted] (1998)
iv. The test guideline for [redacted] (2021).
v. QSAR predictions of BCF with BCF model (Meylan) 1.0.3 for the Substance
vi. QSAR predictions of BCF with BCFBAF v.3.01 model of the potential main degradation products for the Substance.
vii. LogDow predictions with [redacted] Chemicalize model for the Substance.
viii. Information on the topological general characteristics of the Substance.

11.2. Assessment of the information provided in the registration dossier

11.2.1. The log Kow is not a valid descriptor of the bioaccumulation potential of the Substance

116 Under Section 9.3.2., Column 2, first indent of Annex IX to REACH, the study may be omitted if the substance has a low potential for bioaccumulation and/or a low potential to cross biological membranes. A low log Kow (i.e. log Kow < 3) may only be used to support low potential for bioaccumulation if the partitioning to lipids is the sole mechanism driving the bioaccumulation potential of a substance. For some groups of substances (e.g. organometals, ionisable substances, surfactants) other partitioning mechanisms may drive bioaccumulation (e.g. binding to protein/cell membranes). For this reason log Kow is not considered a valid descriptor of the bioaccumulation potential for such substances (Guidance on IRs and CSA, Appendix R.7.10-3).

117 Your registration dossier indicates in section 4.7 that the log Kow is ≤ 3 without further explanation. The Substance is ionisable based on is structure and as also indicated by you under section 4.21 of your registration dossier.

118 Because the substance is ionisable, it belongs to a group of substances where other partitioning mechanisms may drive bioaccumulation. Therefore, Log Kow is not a valid descriptor of the bioaccumulation potential of the Substance and your adaptation is rejected.

119 On this basis, the information requirement is not fulfilled.

11.3. Assessment of the information provided in the comments to the draft decision

11.3.1. Assessment of the weight of evidence approach

120 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.

121 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.

122 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.

123 Relevant information that can be used to support weight of evidence adaptation for the information requirement of Annex IX, Section 9.3.2 includes similar information that is produced by the OECD TG 305. OECD TG 305 requires the study to investigate the following key elements:

1. the uptake rate constant (k1) and loss rate constants including the depuration rate constant (k2), and/or
2. the steady-state bioconcentration factor (BCFSS), and/or
3. the kinetic bioconcentration factor (BCFK), and/or
4. the biomagnification factor (BMF).

124 The source of information (iv) does not provide relevant information on any of the key elements listed above as this is not a study report from a performed test but the testing guideline text used for performing a test. As such, no reporting (e.g. methodology, conditions, results) on an actual test is provided in this source of information.

125 The sources of information (vii) and (viii) do not provide similar information that is produced by the OECD TG 305 and therefore they are considered as not relevant information within the context of the Weight of Evidence approach. However, these sources of information include relevant indicators for assessing low potential for bioaccumulation and low potential to cross biological membranes within the context of Annex IX, Section 9.3.2., column 2. Therefore, ECHA considers this information as relevant under the Annex IX, Section 9.3.2., column 2 as further assessed below.

126 The sources of information (i), (ii), (iii), (v) and (vi) provide relevant information on the key parameters 1 to 3 as listed above.

127 However, the reliability of these sources of information is significantly affected by the following deficiencies:

11.3.1.1. Read-across adaptation rejected for the sources of information (i), (ii) and (iii)

128 ECHA understands that the sources of information (i), (ii) and (iii) included in your weight of evidence approach rely on grouping and read-across approach under Annex XI, Section 1.5. As you rely on a trend analysis to predict the properties of the Substance, ECHA understands that the selected substances follow a regular pattern as result of structural similarity and that you consider those as a group or 'category' of substances.

129 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.

130 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).

131 You do not provide a read-across justification document in your comments.

132 You define the the structural basis for the grouping as "azo-dyes" and "ionic dyestuffs". ECHA understands that this is the applicability domain of the grouping and will assess your predictions on this basis.

133 You predict the properties of the Substance from information obtained from the source substances listed in the respective information source (ii) and (iii). ECHA further noted that the source substances in the information source (i) are not reported.

134 You provide the following reasoning for the prediction of bioaccumulation in aquatic species: "*the applicability of logKow as a predictor of bioaccumulation* […] *in the case of ionic dyestuffs*" is justified.

135 ECHA understands that your read-across hypothesis assumes that different compounds have the same type of effects. You predict the properties of your Substance based on an identified trend within the group.

136 We have identified the following issue(s) with the proposed scope of the grouping:

11.3.1.1.1. Incomplete description of the applicability domain of the category

137 A category (grouping) hypothesis should address "the set of inclusion and/or exclusion rules that identify the ranges of values within which reliable estimations can be made for category members for the given endpoint" (Guidance on IRs and CSA, Section R.6.2.4.1.). Particularly, "the applicability domain of a (sub)category would identify the structural requirements and ranges of physico-chemical, environmental fate, toxicological or ecotoxicological properties within which reliable estimations can be made for the (sub)category members" (Guidance on IRs and CSA, Section R.6.2.1.2.). Therefore, to reliably predict properties within a category the applicability domain should be described including the borders of the category, for which chemicals the category does not hold and a justification for the inclusion and/or exclusion rules.

138 You describe the applicability domain of the substances covered by the grouping as: "azo-dyes" and "ionic dyestuffs".

139 This applicability domain does not introduce unambiguous inclusion/exclusion criteria which would identify the structural requirements and ranges of physico-chemical, environmental fate, toxicological or ecotoxicological properties within which reliable estimations can be made for the (sub)category members.

11.3.1.1.2. Absence of read-across documentation

140 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 include a an explanation why the properties of the Substance may be predicted from information on the source substance(s).

141 You have not provided a read across justification and robust study summaries for the studies conducted with the other substances than the Substance in order to comply with the REACH information requirements.

142 In the absence of such documentation, the properties of the Substance cannot be reliably predicted from the data on the source substances.

11.3.1.1.3. Conclusion on the read-across approach

143 As explained above, the sources of information (i), (ii) and (iii) cannot be considered as reliable sources of information that could contribute to the conclusion on the key parameter investigated by the required study.

11.3.1.2. The provided (Q)SAR adaptation is rejected for sources of information (v) and (vi).

144 Under Annex XI, Section 1.3., the following conditions must be fulfilled whenever a (Q)SAR approach is used:

i. the prediction needs to be derived from a scientifically valid model,
ii. the substance must fall within the applicability domain of the model,
iii. results need to be adequate for the purpose of risk assessment or classification and labelling, and
iv. adequate and reliable documentation of the method must be provided.

145 With regard to these conditions, we have identified the following issues which are common to both sources of information (v) and (vi):

11.3.1.2.1. The selected structure is outside the applicability domain of the models.

146 Under ECHA Guidance R.6.1.5.3., a prediction is within the applicability domain of the model, when, among others, the substance and the structures selected for the prediction falls within descriptor, structural, mechanistic and metabolic domain.

147 However, the selected structures used as input for the QSAR predictions you have provided are outside the mechanistic domain of the model as the model uses log Kow as an input parameter. However, as already explained above, the Substance is surface active and ionisable at environmentally relevant pH. Hence logKow is not a suitable descriptor to predict bioaccumulation because it does not take into account other potential mechanisms of bioaccumulation than lipid storage.

11.3.1.2.2. The predictions are not adequate due to low reliability.

148 Under ECHA Guidance R.6.1.3.4 a prediction is adequate for the purpose of classification and labelling and/or risk assessment when the model is applicable to the chemical of interest with the necessary level of reliability. ECHA Guidance R.6.1.5.3. specifies that, among others, the following condition must be met:

- the model predicts well substances that are similar to the substance of interest

149 The predictions for the selected structure used as input are not reliable because no similar substances to the Substance are included in training set of the model in study.

150 Therefore, you have not demonstrated that the prediction for the Substance is adequate for the purpose of classification and labelling and/or risk assessment.

11.3.1.2.3. Conclusion on the (Q)SAR adaptation

151 In conclusion, the provided predictions cannot be considered as reliable source of information that could contribute to the conclusion on the key parameter investigated by the required study.

11.3.1.3. Conclusion on the Weight of Evidence

152 In summary, the sources of information (i), (ii), (iii), (v) and (vi) provide relevant information on the key elements of this information requirement. However, these sources of information have significant reliability issues as described above and cannot contribute to the conclusion on the information requirement for bioaccumulation in aquatic species.

153 As it is not possible to conclude, based on any source of information alone or considered together, on the information requirement for bioaccumulation in aquatic species. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

11.3.2. Assessment of the adaptation under Annex IX, Section 9.3.2., Column 2

11.3.2.1. The log Dow is not a valid descriptor of the bioaccumulation potential of the Substance (source of information vii.)

154 Under Section 9.3.2., Column 2, first indent of Annex IX to REACH, the study may be omitted if the substance has a low potential for bioaccumulation and/or a low potential to cross biological membranes. A low log Kow (i.e., log Kow < 3) may only be used to support low potential for bioaccumulation if the partitioning to lipids is the sole mechanism driving the bioaccumulation potential of a substance. For some groups of substances (e.g., organometals, ionisable substances, surfactants) other partitioning mechanisms may drive bioaccumulation (e.g., binding to protein/cell membranes). For this reason, log Kow is not considered a valid descriptor of the bioaccumulation potential for such substances (Guidance on IRs and CSA, Appendix R.7.10-3). Similarly, the log Dow would only address the potential for bioaccumulation for substances for which the bioaccumulation is solely driven by lipophilicity. This excludes, for example, situations where the substance is surface active or ionisable at environmental pH (pH 4 – 9).

155 In your comments to the draft decision you provided the source of information (vii) based on which you conclude that the Substances has low likelihood to cross biological membranes based on a calculated Log Dow with [redacted] Chemicalize platform and a comparison with BCF data from National Institute of Technology and Evaluation (Japan). You report the log Dow ranging from 3.96 to 1.09 at pH values of 1.7 and 8 respectively. You then conclude that "as the log D is < 2.5 at pH (7), therefore no Bioaccumulation is expected."

156 The Substance is ionisable and it may interact with cell membranes based on chemical structure. Therefore, log Dow is not a valid descriptor of the bioaccumulation potential of the Substance.

11.3.2.2. Low likelihood to cross biological membranes is not demonstrated (source of information viii.)

157 Under Section 9.3.2., Column 2, first indent, Annex IX to REACH, the study may be omitted if the Substance is unlikely to cross biological membranes. Guidance on IRs and CSA, Section R.7.8.5. explains that there is no scientific basis to define molecular characteristics that would render a substance unlikely to cross biological membranes. In this context, the indicators used for low likelihood of a high bioaccumulation potential (Guidance on IRs and CSA, Section R.11, Figure R.11-4) must be considered, including:

- physico-chemical indicators of hindered uptake due to large molecular size (e.g. Dmax > 17.4 Å and MW > 1100 or MML > 4.3 nm) or high octanol-water partition coefficient (log Kow > 10) or low potential for mass storage (octanol solubility (mg/L) < 0.002 x MW), and

- supporting experimental evidence of hindered uptake (no chronic toxicity for mammals and birds, no chronic ecotoxicity, no uptake in mammalian toxicokinetic studies, very low uptake after chronic exposure).

158 In your comments to the draft decision you provided the source of information (viii) on which you based your conclusion of low likelihood to cross biological membranes based on hindered uptake of the Substance and substantiated with the following physico-chemical indicators:

- the molecular weight of the substance, [redacted] g/mol
- the Dmaximum of 20 Å as calculated by [redacted] Chemicalize platform.

159 The predicted $D_{maximum}$ is not sufficient to demonstrate low likelihood to cross biological membranes. As explained under the Requests 1, 2 and 6 there are standard information

requirement gaps for the Substance that do not allow to conclude on the hindered uptake on the Substance. Therefore, you have not demonstrated that the Substance has low likelihood to cross biological membranes. Therefore, the adaptation is rejected.

160 On this basis, the information requirement is not fulfilled.

11.4. Study design and test specifications

161 Bioaccumulation in fish: aqueous and dietary exposure (Method EU C.13 / OECD TG 305) is the preferred test to investigate bioaccumulation (Guidance on IRs and CSA, Section R.7.10.3.1.). Exposure via the aqueous route (OECD TG 305-I) must be conducted unless it can be demonstrated that:

- a stable and fully dissolved concentration of the test material in water cannot be maintained within ± 20% of the mean measured value, and/or
- the highest achievable concentration is less than an order of magnitude above the limit of quantification (LoQ) of a sensitive analytical method.

162 This test set-up is preferred as it allows for a direct comparison with the B and vB criteria of Annex XIII of REACH.

163 You may only conduct the study using the dietary exposure route (OECD 305-III) if you justify and document that testing through aquatic exposure is not technically possible as indicated above. You must then estimate the corresponding BCF value from the dietary test data according to Annex 8 of the OECD 305 TG and OECD Guidance Document on Aspects of OECD TG 305 on Fish Bioaccumulation (ENV/JM/MONO(2017)16).

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

The information requirement for an Extended one-generation reproductive toxicity study (EOGRTS; Annexes IX or X, Section 8.7.3.) is not addressed in this decision. This may be addressed in a separate decision once the information from the Sub-chronic toxicity study (90-day) requested in the present decision is provided; due to the fact that the results from the 90-day study is needed for the design of the EOGRTS. Similarly the information requirement for a Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.) is not addressed in this decision; as the EOGRTS will cover the same parameters.

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 21 April 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 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.

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.

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 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.

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]
[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[4].

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 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[5].

[4] https://echa.europa.eu/practical-guides
[5] https://echa.europa.eu/manuals

2. General recommendations for conducting and reporting new tests

2.1. Strategy for the PBT/vPvB assessment

Under Annex XIII, the information must be based on data obtained under conditions relevant for the PBT/vPvB assessment. You must assess the PBT properties of each relevant constituent of the Substance present in concentrations at or above 0.1% (w/w) and of all relevant transformation/degradation products. Alternatively, you would have to justify why you consider these not relevant for the PBT/vPvB assessment.

You are advised to consult Guidance on IRs & CSA, Sections R.7.9, R.7.10 and R.11 on PBT assessment to determine the sequence of the tests needed to reach the conclusion on PBT/vPvB. The guidance provides advice on 1) integrated testing strategies (ITS) for the P, B and T assessments and 2) the interpretation of results in concluding whether the Substance fulfils the PBT/vPvB criteria of Annex XIII.

In particular, you are advised to first conclude whether the Substance fulfils the Annex XIII criteria for P and vP, and then continue with the assessment for bioaccumulation. When determining the sequence of simulation degradation testing you are advised to consider the intrinsic properties of the Substance, its identified uses and release patterns as these could significantly influence the environmental fate of the Substance. You must revise your PBT assessment when the new information is available.