~~Confidential~~

Helsinki, 22 January 2024

Addressee(s)
Registrant(s) of JS (27178-16-1/248-299-9) as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
29 March 2023

Registered substance subject to this decision ("the Substance")
Substance name: Diisodecyl adipate
EC/List number: 248-299-9

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 ***29 April 2027***.

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

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

1. Skin sensitisation (Annex VII, Section 8.3.)

   a) in vitro/in chemico skin sensitisation information on molecular interactions with skin proteins (OECD TG 442C), inflammatory response in keratinocytes (OECD TG 442D) and activation of dendritic cells (OECD TG 442E) (Annex VII, Section 8.3.1.);

   and

   b) only if the *in vitro/in chemico* test methods specified under point a) above are not applicable for the Substance or the results obtained are not adequate for classification and risk assessment, *in vivo* skin sensitisation (Annex VII, Section 8.3.2.; test method: EU B.42./OECD TG 429).

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

2. Justification for an adaptation of the short-term repeated dose toxicity study (28 days) (Annex VIII, Section 8.6.1., Column 2) based on the request 5 below.

   If the sub-chronic toxicity study (90 days) is not requested:

   Short-term repeated dose toxicity (28 days) (Annex VIII, Section 8.6.1.) by oral route, in rats, to be combined with the screening for reproductive/developmental toxicity requested below.

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

4. Long-term toxicity testing on fish (triggered by Annex VIII, Section 9.1.3., column 2; test method: EU C.47./OECD TG 210)

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

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

6. 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).

7. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: EU C.47./OECD TG 210)

The reasons for the request(s) are explained in Appendix 1.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you in accordance with Articles 10(a) and 12(1) of REACH. The addressees of the decision and their corresponding information requirements based on registered tonnage band are listed in Appendix 3.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

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

You must follow the general requirements for testing and reporting new tests under REACH, see Appendix 4.

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Mike Rasenberg, Director of Hazard Assessment

Appendix 1: Reasons for the request(s)
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 request(s)

Reasons common to several requests

0.1. Read-across adaptation rejected

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

- Skin sensitisation (Annex VII, Section 8.3.)
- Short-term repeated dose toxicity (28 days) (Annex VIII, Section 8.6.1.)
- Sub-chronic toxicity study (90 days) (Annex IX, Section 8.6.2.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Pre-natal developmental toxicity study, one species (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).

5 You provide a read-across justification document in IUCLID Section 13.2

0.1.1. Scope of the grouping of substances

0.1.1.1. Category definition

6 In this decision, the following abbreviations are used for the category members:

- Diisodecyl adipate / EC 248-299-9 / CAS 27178-16-1 (the Substance)
- Diisooctyl adipate / EC 215-553-5 / CAS 1330-86-5 (source substance 1)
- Bis(2-ethylhexyl) adipate (DEHA) / EC 203-090-1 / CAS 103-23-1 (source substance 2)
- Diisononyl adipate / EC 251-646-7 / CAS 33703-08-1 (source substance 3)
- Bis(tridecyl) adipate / EC 241-029-0 / CAS 16958-92-2 (source substance 4)

7 You justify the grouping of the substances as: "*Due to the structural similarities and the consistent trend in physico-chemical properties, toxicological properties, ecotoxicological properties and toxicokinetic behaviour, these five substances are considered as a category of substances[…]*".

8 You define the the structural basis for the grouping as: "*This category consists of diisodecyl adipate, diisooctyl adipate, bis(2-ethylhexyl) adipate, diisononyl adipate and bis(tridecyl) adipate, which have similar chemical structures (see Table 1 below for details). These chemicals are all diester derivatives of the dicarboxylic acid, adipic acid (C6). The parent alcohols have carbon chain lengths of C8 to C15 (linear and branched).*"

9 ECHA understands that this is the applicability domain of the grouping and will assess your predictions on this basis

0.1.2. Predictions for toxicological properties

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

11 You predict the properties of the Substance from information obtained from the following source substances: category member substances EC 203-090-1 (source substance 2), EC 251-646-7 (source substance 3) and EC 241-029-0 (source substance 4).

12 You provide the following reasoning for the prediction of toxicological properties:

13 "*Due to the structural similarities and the consistent trend in physico-chemical properties, toxicological properties, ecotoxicological properties and toxicokinetic behaviour, these five substances are considered as a category of substances*".

14 You state the following prediction for the mammalian toxicological profile for the category members (including the Substance):

15 "*The category members show no acute oral, dermal or inhalation toxicity and no skin irritation, eye irritation or skin sensitisation. These five substances also show no significant systemic toxicity relevant to humans after repeated oral, inhalative and dermal exposure and they are not mutagenic or clastogenic. In addition, they have shown no relevant reproduction toxicity/development toxicity.*"

16 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.

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

0.1.2.1. Missing supporting information to compare the properties of the substances

18 Annex XI, Section 1.5 requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information should strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substances (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

19 Supporting information must include information to compare properties of the source substances and information on the impact of exposure parent compounds on the prediction.

20 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar source substances cause the same type of effects. In this context, relevant, reliable and adequate information allowing to compare the properties of the source substances is necessary to confirm that the substances cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration with the Substance and the source substances.

21 For skin sensitisation you have provided:

- data obtained from Qualitative or Quantitative Structure-Activity Relationships ((Q)SARs) approach with a prediction using the OASIS Times Mix with source substances 2 and 3 (EC 203-090-1 and EC 251-646-7)

22 No skin sensitisation information is available for the Substance or for the source substances 1 and 4 (EC 215-553-5 and EC 241-029-0).

23 For repeated dose toxicity you have provided:

- an oral sub-chronic toxicity study in rats with the source substance 2 (EC 203-090-1)
- an oral sub-chronic toxicity study in mice with the source substance 2 (EC 203-090-1)
- a dermal sub-chronic toxicity study with the source substance 4 (EC 241-029-0)

24 No repeated dose toxicity information is available for the Substance or for the source substances 1 and 3 (EC 215-553-5 and EC 251-646-7).

25 For reproductive/developmental toxicity you have provided:

- a one-generation reproduction toxicity study with the source substance 2 (EC 203-090-1)
- a pre-natal developmental toxicity study with the source substance 2 (EC 203-090-1)

26 Bridging studies of comparable design and duration for the Substance and of the source substances as listed above, are missing for skin sensitisation, repeated dose toxicity, and for reproductive/developmental toxicity.

27 In addition, specific reasons why these studies cannot be considered reliable are explained further below under the relevant information requirement in sections 1. Skin Sensitisation, 2. Short term repeat dose toxicity study (28-day), and 5. Sub chronic toxicity study (90-day). Thus the data set reported in the technical dossier does not include relevant, reliable and adequate information for the source substances to support your read-across hypothesis.

28 In the absence of such information, you have not established that the Substance and the source substances are likely to have similar properties. Therefore you have not provided sufficient supporting information to scientifically justify the read-across.

0.1.2.2. Read-across hypothesis contradicted by existing data

29 Annex XI, Section 1.5. requires that whenever read-across is used adequate and reliable documentation of the applied method must be provided. Such documentation must provide supporting information to scientifically justify the read-across explanation for prediction of properties. The set of supporting information must strengthen the rationale for the read-across in allowing to verify the crucial aspects of the read-across hypothesis and establishing that the properties of the Substance can be predicted from the data on the source substance(s) (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.).

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

31 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.

32 In your read-across justification you predict no reproduction toxicity/development toxicity for the category substances. However, data provided in your dossier indicate test item related reproductive/developmental toxic effects (including decreased litter size or (pre-implantation) litter losses and skeletal defects) induced by the source substance 2 (EC 203-

090-1) in the one-generation reproduction toxicity and pre-natal developmental toxicity studies. This contradicts your prediction for no hazardous effects.

33 The available set of data on the Substance and on the source substances indicates possible human health hazards which contradicts your read-across hypothesis whereby the Substance and source substances cause the same type of effects and induce no relevant toxicities. However, you have not supported and scientifically justified why the observed differences in the toxicological properties do not affect your read-across hypothesis.

0.1.2.3. Inadequate or unreliable source studies

34 According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across must:

(1) be adequate for the purpose of classification and labelling and/or risk assessment;
(2) have adequate and reliable coverage of the key parameters addressed in the corresponding study that shall normally be performed for a particular information requirement;
(3) cover an exposure duration comparable to or longer than the corresponding study that shall normally be performed for a particular information requirement if exposure duration is a relevant parameter.

35 Specific reasons why the studies on the source substances do not meet these criteria are explained further below under the applicable information requirement in sections 1. Skin Sensitisation, 2. Short term repeat dose toxicity study (28-day), and 5. Sub chronic toxicity study (90-day). Therefore, no reliable predictions can be made for these information requirements

0.1.3. Conclusion on the read-across approach

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

0.2. Weight of Evidence

37 Besides specifically claiming an adaptation using Annex XI, Section 1.5. (grouping of substances and read-across approach), you have indicated the adequacy of some of the endpoint study records as weight of evidence. Annex XI, section 1.2 (Weight of Evidence) requires that adequate and reliable documentation is provided to describe your weight of evidence approach. You have however not submitted any explanation why the sources of information provide sufficient weight of evidence leading to the conclusion/ assumption that the Substance has or has not a particular dangerous property. ECHA understands therefore you intend to adapt the information using Annex XI, Section 1.5. (grouping of substances and read-across approach) and has assessed the information on that basis.

Reasons related to the information under Annex VII of REACH

1. Skin sensitisation

38 Skin sensitisation is an information requirement under Annex VII, Section 8.3. Under Section 8.3., Column 1, the registrants must submit information allowing (1) a conclusion whether the substance is a skin sensitiser and (2) whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

1.1. Information provided

39 You have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on predictions from the following substances:

(i) a prediction using the OASIS Times Mix 2.26.3 (2010) with the source substance 2 (EC 203-090-1)

(ii) a prediction using the OASIS Times Mix 2.26.3 (2008) with the source substance 3 (EC 251-646-7)

1.2. Assessment of the information provided

1.2.1. Read-across adaptation rejected

40 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 issues addressed below.

41 As discussed in Section 0.1, if the grouping concept is applied then in all cases the results to be read across must:

- be adequate for the purpose of classification and labelling and/or risk assessment;
- have adequate and reliable coverage of the key parameters addressed in the corresponding study that shall normally be performed for a particular information requirement;

42 This is not the case here for the following reasons.

1.2.1.1. Inadequate documentation of the prediction (QPRF)

43 Guidance on IRs and CSA R.6.1.6.3. states that the information specified in or equivalent to the (Q)SAR Prediction Reporting Format document (QPRF) must be provided to have adequate and reliable documentation of the applied method. For a QPRF this includes, among others:

- a precise identification of the substance modelled;
- the relationship between the modelled substance and the defined applicability domain;
- the identities of close analogues, including considerations on how predicted and experimental data for analogues support the prediction.

44 You provided the following information about the prediction: "*A quantitive structure-activity relationship (QSAR) system for the estimation of the skin sensitization potency that incorporates skin metabolism and consideres the potential of parent chemicals and/or their activated metabolites to react with skin proteins. A chemically divers training set was used and their skin sensitization potency assigned to one of three classes*." And based on this

you predict "*The QSAR program calculated a negative sensitization potential of the test substance*."The information you provided about the prediction lacks the following elements:

- no SMILES (Simplified molecular-input line-entry system) input provided for the analogue substances;
- no information on the relationship between the modelled substance and the defined applicability domain;
- no information provided on the used analogues and how predicted negative sensitization potential of the analogues support the prediction for the target substance

45 In absence of such information, ECHA cannot establish that the prediction can be used to meet this information requirement.

1.2.1.2. Lack of documentation of the model (QMRF)

46 Under Appendix C of the OECD Guidance document on the validation of (Q)SAR models (ENV/JM/MONO(2007)2) and Guidance on IRs and CSA R.6.1.6.3., adequate and reliable documentation must include a (Q)SAR Model Reporting Format document (QMRF) which reports, among others, the following information:

- the predicted endpoint, including information on experimental protocol and data quality for the data used to develop the model;
- an unambiguous definition of the algorithm, the descriptor(s) of the model and its applicability domain,
- an estimate of the goodness-of-fit and of the predictivity of the model, including information on training set and validation statistics.

47 You have not provided information about the model.

48 In absence of such information, ECHA cannot establish that the model can be used to meet this information requirement.

49 Therefore, the information requirement is not fulfilled.

1.3. Study design

50 To fulfil the information requirement for the Substance, information on molecular interaction with skin proteins and inflammatory response in keratinocytes and activation of dendritic cells (OECD TG 442C and OECD TG 442D and OECD TG 442E) must be provided. Furthermore an appropriate risk assessment is required if a classification of the Substance as a skin sensitiser (Cat 1A or 1B) is warranted.

51 In case no conclusion on the skin sensitisation potency can be made for the Substance based on the existing data or newly generated in vitro/in chemico data, in vivo skin sensitisation study must be performed and the murine local lymph node assay (EU Method B.42/OECD TG 429) is considered as the appropriate study for the potency estimation.

52 In your comments to the draft decision, you agree to perform an OECD TG 429 study and you will provide a justification for the selection of the test guideline.

Reasons related to the information under Annex VIII of REACH

2. Short-term repeated dose toxicity (28 days)

53 A short-term repeated dose toxicity study (28 days) is an information requirement under Annex VIII, 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 or a general adaptation rule under Annex XI.

2.1. Information provided

54 You have have not specifically claimed for an adaptation to omit the short term repeated dose toxicity study but ECHA understands that you have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on experimental data from the following substances:

(i) a sub-chronic oral toxicity study in rats (1982) with the source substance 2 EC 203-090-1;

(ii) a sub-chronic oral toxicity study in mice (1982) with the source substance 2 EC 203-090-1

(iii) a sub-chronic dermal toxicity study in rats (1986) with the source substance 4, EC 241-029-0.

2.2. Assessment of the information provided

2.2.1. Read-across adaptation rejected

55 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, the studies relied on are not reliable for the reasons explained in request 5.

56 Based on the above, your adaptation is rejected.

57 Therefore, the information requirement is not fulfilled.

2.3. Study design

58 When there is no information available neither for the 28-day repeated dose toxicity (EU B.7, OECD TG 407), nor for the screening study for reproductive/developmental toxicity (OECD TG 421 or TG 422), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to ensure that unnecessary animal testing is avoided (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

59 The study design is addressed in request 3.

2.3.1. Justification for an adaptation of the short-term repeated dose toxicity study (Annex VIII, Section 8.6.1., Column 2)

60 The present decision requests the registrants concerned to generate and submit a reliable sub-chronic toxicity study (90 days) (see request 5).

61 According to Annex VIII, Section 8.6.1., Column 2 and to prevent unnecessary animal testing, a short-term toxicity study (28 days) does not need to be conducted. Therefore, to comply with the information requirement in Annex VIII, Section 8.6.1., you are requested to provide a justification for adaptation, as provided in Annex VIII, Section 8.6.1., Column 2.

62 In case the adopted decision no longer contains a request for a 90-day study, you are required to provide a 28-day study.

63 Therefore, you are requested to either submit:

- a justification for the adaptation according to Annex VIII, Section 8.6.1., Column 2, based on request 5; or
- a 28-day study as per the study design described in 3 in case the 90-day study is not requested in the adopted decision.

3. Screening study for reproductive/developmental toxicity

64 A screening study for reproductive/developmental toxicity study (OECD 421 or OECD 422) is an information requirement under Annex VIII, Section 8.7.1.

3.1. Information provided

65 You have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on experimental data from the following substance:

a one generation reproduction toxicity study (1988) with the source substance 2 EC 209-090-1.

3.2. Assessment of the information provided

3.2.1. Read-across adaptation rejected

66 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.

67 Therefore, the information requirement is not fulfilled.

3.3. Study design

68 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.

69 As the Substance is a liquid, the study must be conducted with oral administration of the Substance (Annex VIII, Section 8.7.1., Column 1).

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

71 In case the adopted decision no longer contains a request for a sub-chronic (90 days) study (e.g. as a result of an overall tonnage band change of the joint submission), a screening study for reproductive/developmental toxicity performed according to the OECD TG 422 is preferred.

72 When there is no information available neither for the 28-day repeated dose toxicity study (EU B.7, OECD TG 407), nor for the screening study for reproductive/developmental toxicity (OECD TG 421 or TG 422), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to ensure that unnecessary animal testing is avoided (Guidance on IRs and CSA, Section R.7.6.2.3.2.).

73 The information requirement for the 28-day repeated dose toxicity study is not fulfilled for the reasons explained under request 2.

74 Therefore, a study according to the test method EU B.64/OECD TG 422 must be performed in rats.

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

4. Long-term toxicity testing on fish

76 Short-term toxicity testing on fish is an information requirement under Annex VIII, Column 1, Section 9.1.3. However, long-term toxicity testing on fish may be required by the Agency (Section 9.1.3., Column 2) if the substance is poorly water soluble, i.e. solubility below 1 mg/L.

4.1. Triggering of the information requirement

77 In the provided study according to EU Method A.6 (2001), the saturation concentration of the Substance in water was determined to be <0.1 mg/L.

78 Therefore, the Substance is poorly water soluble and information on long-term toxicity on fish must be provided.

4.2. Information requirement not fulfilled

79 The information provided, its assessment and the specifications of the study design are addressed under request 7 (Long-term toxicity testing on fish).

Reasons related to the information under Annex IX of REACH

5. Sub-chronic toxicity study (90 days)

80 A sub-chronic toxicity study (90 days) is an information requirement under Annex IX, Section 8.6.2.

5.1. Information provided

81 You have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on experimental data from the following substances:

(i) a sub-chronic oral toxicity study in rats (1982) with the source substance 2 EC 203-090-1;

(ii) a sub-chronic oral toxicity study in mice (1982) with the source substance 2 EC 203-090-1

(iii) a sub-chronic dermal toxicity study in rats (1986) with the source substance 4 EC 241-029-0.

5.2. Assessment of the information provided

5.2.1. Read-across adaptation rejected

82 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.

5.2.1.1. Inadequate or unreliable studies on the source substances

83 Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed and cover an exposure duration comparable to or longer than the one specified in the test guideline for the corresponding study that shall normally be performed for a particular information requirement, in this case OECD TG 408 (studies i and ii), or OECD TG 411 (study iii). Therefore, the following specifications must be met:

a) testing is performed with at least three dose levels (unless conducted at the limit dose) and with concurrent controls;

b) dosing of the Substance is performed daily for a minimum of 90 days for 7 days per week;

c) body weight and food consumption is measured at least weekly;

d) haematological and clinical biochemistry tests are performed as specified in paragraphs 30-38 of OECD TG 408;

e) the oestrus cycle in females is examined at necropsy;

f) terminal organ and body weights are measured;

g) gross pathological examinations as specified in paragraphs 43-46 of OECD TG 408;

h) full histopathology is performed as specified in paragraphs 47-49 of OECD TG 408;

i) according to OECD TG 411, the test substance should be held in contact with the skin in between the applications with a porous gauze dressing and non-irritating tape.

84 In studies (i) and (ii):

c) there is no information on how frequently food consumption was measured;

d) haematology and clinical biochemistry were not performed;

e) oestrus cyclicity was not assessed;

f) terminal organ weights were not assessed and thus and organ/body weight ratios were not recorded;

g) data for organs for which the pathological examination was perfomed is missing;

h) data for organs for which the histopathological examination was perfomed is missing.

85 In study (iii)

a) only two dose levels were described;

b) dermal dosing was applied only for 5 days/week (24h/d) for a period of 90 days instead of 7 days per week and no justification for this deviation was given;

i) the skin was not covered between the applications.

86 The information provided does not have adequate and reliable coverage of the key parameters of OECD TG 408/411.

5.2.1.2. Inapproriate route of administration

87 Under Annex IX, Section 8.6.2, column 2, paragraph 7, the appropriate route of administration is dermal only if:

a) skin contact in production and/or use is likely; and

b) the physicochemical properties suggest a significant rate of absorption through the skin; and

c) one of the following conditions is met:

- toxicity is observed in the acute dermal toxicity test at lower doses than in the oral toxicity test,
- systemic effects or other evidence of absorption is observed in skin and/or eye irritation studies,
- *in vitro* tests indicate significant dermal absorption,
- significant dermal toxicity or dermal penetration is recognised for structurally-related substances.

88 In study (iii):

- the acute dermal toxicity test did not show toxicity at lower doses than in acute oral studies;
- no relevant systemic toxicity or other indications of absorption were observed in irritation studies (only mild local dermal irritation was reported);
- no *in vitro* tests indicating significant dermal absorption were provided;

- no data on significant dermal toxicity or dermal penetration for structurally-related substances were provided.

89 No justification was provided why the dermal route was selected in study (iii). Furthermore, the data provided in the the technical dossier and in the chemical safety report in IUCLID section 13.1. provide no evidence that the above criteria for selecting dermal route are met.

90 Based on the above, the studies do not provide an adequate and reliable coverage of the key parameters specified in the OECD TG 408. Therefore these studies are not an adequate basis for your read-across predictions.

5.3. Study design

91 Following the criteria provided in Annex IX, Section 8.6.2., Column 2, and considering the Guidance on IRs and CSA, Section R.7.5.6.3.2., the oral route is the most appropriate route of administration to investigate repeated dose toxicity of the Substance, because the Substance is a liquid of very low vapour pressure. Uses with industrial and consumer spray application are reported in the chemical safety report but potential inhalation-specific effects are already addressed by deriving a long-term DNEL for inhalation. Risk management measures for the safe use of the substance are addressed in the CSR.

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

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

6. Pre-natal developmental toxicity study in one species

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

6.1. Information provided

95 You have adapted this information requirement by using Annex XI, Section 1.5. (grouping of substances and read-across approach) based on experimental data from the following substances:

(i) a pre-natal developmental toxicity study in rats (1988) with the source substance 2 EC 203-090-1.

6.2. Assessment of the information provided

6.2.1. Read-across adaptation rejected

96 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.

97 Therefore, the information requirement is not fulfilled.

6.3. Study design

98 A PNDT study according to the test method OECD TG 414 should be performed in rats or rabbits as preferred species.

99 As the Substance is a liquid, the study must be conducted with oral administration of the Substance (Annex IX, Section 8.7.2., Column 1).

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

7. Long-term toxicity testing on fish

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

7.1. Information provided

102 You have adapted this information requirement and in support of your adaptation, you provide the following justification:

(i) "In acute aquatic toxicity studies with read-across substances, the LC50/EC50 values were greater than the maximum water solubility of the substances. Also, long-term studies with read-across substances representing two trophic levels (algae and daphnia) did not show any effects up to the water solubility of the substance. Furthermore, it is not assumed that fish are more sensitive to this substance than algae or daphnia based on the available acute data. Therefore further testing is not necessary."

7.2. Assessment of information provided

103 We have assessed this information and identified the following issue:

7.2.1. Your justification to omit the study has no legal basis

104 A registrant may only adapt this information requirement based on the general rules set out in Annex XI.

105 It is noted that Column 2 of Annex IX, Section 9.1, does not allow omitting the need to submit information on long-term toxicity to fish under Column 1 (Decision of the Board of Appeal in case A-011-2018).

106 Your justification to omit this information does not refer to any legal ground for adaptation under Annex XI to REACH and the legal basis you are relying on for your intended adaptation is not apparent to ECHA.

107 In addition, with regard to the arguments about lack of potential for aquatic toxicity and sensitivity of aquatic species, we note that the Substance is poorly water soluble and therefore short-term toxicity studies do not allow to conclude on fish toxicity.

108 Therefore, you have not demonstrated that this information can be omitted.

109 Therefore, the information requirement is not fulfilled.

7.3. Your comments to the draft decision

110 In your comments to the draft decision you agree with the request.

7.4. Study design

111 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.).

112 The Substance is difficult to test due to the low water solubility (<0.1 mg/L) and adsorptive properties: Log K_{oc} = 6.9 (value estimated with QSAR - EPI Suite, v4.11, KOCWIN, v2.00).

OECD TG 210 specifies that, for difficult to test substances, you mustc consider the approach described in OECD GD 23 or other approaches, if more appropriate for your substance. In all cases, the approach selected must be justified and documented. Due to the properties of Substance, it may be difficult to achieve and maintain the desired exposure concentrations. Therefore, you must monitor the test concentration(s) of the Substance throughout the exposure duration and report the results. If it is not possible to demonstrate the stability of exposure concentrations (i.e. measured concentration(s) not within 80-120% of the nominal concentration(s)), you must express the effect concentration based on measured values as described in OECD TG 210. In case a dose-response relationship cannot be established (no observed effects), you must demonstrate that the approach used to prepare test solutions was adequate to maximise the concentration of the Substance in the test solution.

113 For multi-constituents/UVCBs, the analytical method must be adequate to monitor qualitative and quantitative changes in exposure to the dissolved fraction of the test material during the test (e.g. by comparing mass spectral full-scan GC or HPLC chromatogram peak areas or by using targeted measures of key constituents or groups of constituents).

114 If you decide to use the Water Accommodated Fraction (WAF) approach, in addition to the above, you must:

- use loading rates that are sufficiently low to be in the solubility range of most constituents (or that are consistent with the PEC value). This condition is mandatory to provide relevant information for the hazard and risk assessment (Guidance on IRs and CSA, Appendix R.7.8.1-1, Table R.7.8-3);
- provide a full description of the method used to prepare the WAF (including, among others, loading rates, details on the mixing procedure, method to separate any remaining non-dissolved test material including a justification for the separation technique);
- prepare WAFs separately for each dose level (i.e. loading rate) and in a consistent manner.

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).
Guidance for monomers and polymers; ECHA (2023).
***Guidance on intermediates*;** ECHA (2010).
All guidance documents are available online: https://echa.europa.eu/guidance-documents/guidance-on-reach

Read-across assessment framework (RAAF)

RAAF, 2017 Read-across assessment framework (RAAF); ECHA (2017).
RAAF UVCB, 2017 Read-across assessment framework (RAAF) – considerations on multi- constituent substances and UVCBs; ECHA (2017).

The RAAF and related documents are available online:
https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

***OECD Guidance documents* (OECD GDs)**

OECD GD 23 Guidance document on aquatic toxicity testing of difficult substances and mixtures; No. 23 in the OECD series on testing and assessment, OECD (2019).
OECD GD 29 Guidance document on transformation/dissolution of metals and metal compounds in aqueous media; No. 29 in the OECD series on testing and assessment, OECD (2002).
OECD GD 150 Revised guidance document 150 on standardised test guidelines for evaluating chemicals for endocrine disruption; No. 150 in the OECD series on testing and assessment, OECD (2018).
OECD GD 151 Guidance document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test; No. 151 in the OECD series on testing and assessment, OECD (2013).

Appendix 2: Procedure

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

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

The compliance check was initiated on 11 August 2022.

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

ECHA took into account your comments and did not amend the request(s).

The deadline of the decision is set based on standard practice for carrying out OECD TG tests. It has been exceptionally extended by 12 months from the standard deadline granted by ECHA to take into account currently longer lead times in contract research organisations.

In your comments you explained that following the tonnage band downgrade of the current lead registrant negotiations on transferring the lead registrant role have started. ECHA notes that the information requirements set out in this decision apply to each individual addressee according to their applicable tonnage band. The fact that the lead registrant role is currently unclear does not have any bearing on the obligation of each addressee of this decision to comply with the applicable information requirements by the deadline set out in this decision.

The registrant who will perform a test on behalf of the other registrants must be selected among the addressees of the decision to which the request applies. Under Article 53(1) of REACH, if ECHA is not informed of an agreement, ECHA will designate a registrant to perform the test on behalf of all registrants required to perform the same test.

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix 3: Addressee(s) of this decision and their corresponding information requirements

In accordance with Articles 10(a) and 12(1) of REACH, the information requirements for individual registrations are defined as follows:

- the information specified in Annex VII to REACH, for registration at 1-10 tonnes per year (tpa), or as a transported isolated intermediate in quantity above 1000 tpa;
- the information specified in Annexes VII and VIII to REACH, for registration at 10-100 tpa;
- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa;
- the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]
[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]
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[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 (https://echa.europa.eu/practical-guides).

(4) Under the introductory part of Annexes VII/VIII/IX/X to REACH, where a test method offers flexibility in the study design, for example in relation to the choice of dose levels or concentrations, the chosen study design must ensure that the data generated are adequate for hazard identification and risk assessment.

1.2 Test material

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/group of constituents on the test results for the endpoint to be assessed. For example, if a constituent/group of constituents of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/group of constituents.

(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 the careful identification and description of the characteristics of the Tests Materials in accordance with OECD GLP (ENV/MC/CHEM(98)16) and EU Test Methods Regulation (EU) 440/2008 (Note, Annex), namely all the constituents must be identified as far as possible as well as their concentration. Also any constituents that have harmonised classification and labelling according to the CLP Regulation must be identified and quantified using the appropriate analytical methods.

With that detailed information, ECHA can confirm whether the Test Material is relevant for the Substance 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 (https://echa.europa.eu/manuals).