~~Confidential~~

Helsinki, 13 February 2024

Addressees
Registrants of joint submission of NEDS as listed in Appendix 3 of this decision

Date of submission of the dossier subject to this decision
10 September 2015

Registered substance subject to this decision ("the Substance")
Substance name: N,N'-ethylenedi(stearamide)
EC/List number: 203-755-6

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 ***21 May 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).

2. *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, OECD TG 471).

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

3. *In vitro* micronucleus study (Annex VIII, Section 8.4.2., test method: OECD TG 487). The aneugenic potential of the Substance must be assessed with an additional control group for aneugenicity on top of the control group for clastogenicity, if the Substance induces an increase in the frequency of micronuclei.

4. Only if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained, *in vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: EU B.17./OECD TG 476 or EU B.67./OECD TG 490).

5. 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.

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

7. Long-term toxicity testing on fish (triggered by Annex VIII, Section 9.1.3., column 2; 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 provided information derived from experimental data from groups of substances using the OECD QSAR Toolbox and flagged the information as QSAR for the following standard information requirements:

- Skin sensitisation (Annex VII, Section 8.3.)
- *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

2 As the groups of substances are used as source substances to predict the property of the Substance, we understand that you have adapted the standard information requirements under Annex XI, Section 1.5 of REACH (grouping and read-across).

3 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.

4 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.

5 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. Scope of the grouping of substances (category)

6 For the purpose of this decision, the following abbreviations are used for the category members:

7 For skin sensitisation:

- Cat. member No. 1, CAS 40618-31-3
- Cat. member No. 2, CAS 40618-31-3
- Cat. member No. 3, no CAS number, tert-butyl ((7r,9r)-9-{2-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1h-pyrrol-1-yl]ethyl}-6,10-dioxasprio[4.5]dec-7yl)acetate
- Cat. member No. 4, CAS 68227-78-1
- Cat. member No. 5, CAS 6041-94-7

For *in vitro* gene mutation study in mammalian cells:

- Cat. member No. 6, CAS 71566-54-6
- Cat. member No. 7, CAS 35869-64-8
- Cat. member No. 8, CAS 22094-93-5
- Cat. member No. 9, CAS 31775-20-9
- Cat. member No. 10, CAS 6358-37-8

For screening study for reproductive/developmental toxicity study:

- Cat. member No. 11, CAS 22094-93-5
- Cat. member No. 12, CAS 6448-95-9
- Cat. member No. 13, CAS 31775-20-9
- Cat. member No. 14, CAS 6358-37-8
- Cat. member No. 15, CAS 5102-83-0

8 You justify the grouping of the substances by the following statement: "[the selected substances are the] *nearest neighbours compared by prediction descriptors*".

9 You have provided no definition of the applicability domain of your category.

10 We have identified the following issue with the proposed scope of the grouping:

0.1.1.1. Incomplete description of the applicability domain of the category

11 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.

12 You describe the applicability domain of the substances covered by the grouping as: "*Category members are single chemicals or mixtures and are selected based on the profile of the target chemical. Only chemicals having experimental data are listed in the category*". You have not provided a description of the structural requirements and ranges of physico-chemical, environmental fate, toxicological or ecotoxicological properties for the category.

13 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.

0.1.2. Predictions for toxicological properties

14 You predict the properties of the Substance from information obtained from several source substances. The list of source substances corresponding to the prediction under the respective standard information requirement under consideration is provided under section 0.1.1.

15 You provide the following reasoning for the prediction of toxicological properties: "*The substances have a similar profile based on ECHA CHEM*".

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 substances.

0.1.2.1. Missing supporting information to compare properties of the substances

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

18 Supporting information must include (bridging) studies to compare the properties of the category members.

19 As indicated above, your read-across hypothesis is based on the assumption that the structurally similar source substance(s) cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the source substance(s) 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 for the Substance and of the source substance(s).

20 For the source substances, you provide the reference to the data that is used in the prediction in the registration dossier. Apart from the reference to those data, you do not provide any read-across justification explaining why the properties for the source substances can be used to predict the properties of the Substance. In addition, you do not include any information on the Substance that would confirm that the Substance and the source substances cause the same type of effects.

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

0.1.2.2. Missing robust study summaries

22 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 robust study summary for each source study used in the adaptation.

23 Robust study summary must provide a detailed summary of the objectives, methods, results and conclusions of a full study report providing sufficient information to make an independent assessment of the study (Article 3(28)).

24 ECHA understands that your read-across adaptation relies on experimental data. You have not provided robust study summaries of the tests conducted with the source substances, whose results are the basis for your prediction.

25 You have not provided detailed information on the methods, results and conclusions, allowing for an independent assessment of the source studies. Therefore, you have failed to provide a robust study summary for each source study used in the adaptation as required by Annex XI, Section 1.5.

0.1.3. Conclusion

26 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.

Reasons related to the information under Annex VII of REACH

1. Skin sensitisation

27 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

28 You have provided information on a group of substances derived from the OECD QSAR Toolbox version 3.3 for skin sensitisation.

1.2. Assessment of the information provided

1.2.1. Assessment whether the Substance causes skin sensitisation

1.2.1.1. Read-across adaptation rejected

29 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.

30 On this basis, the information provided does not contribute to the assessment whether the Substance causes skin sensitisation.

1.2.2. No assessment of potency

31 To be considered compliant and enable a conclusion in cases where the substance is considered to cause skin sensitisation, the information provided must also allow a conclusion whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A).

32 As the currently available data does not allow to conclude whether the Substance causes skin sensitisation (see section 1.2.1 above), this condition cannot be assessed.

33 Therefore, the information requirement is not fulfilled.

1.3. Study design

34 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.

35 In case no conclusion on the skin sensitisation potency can be made for the Substance based on the existing data or newly generated 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.

2. *In vitro* gene mutation study in bacteria

36 An *in vitro* gene mutation study in bacteria is an information requirement under Annex VII, Section 8.4.1.

2.1. Information provided

37 You have provided an *in vitro* gene mutation study in bacteria (2011) with the Substance.

2.2. Assessment of the information provided

2.2.1. The provided study does not meet the specifications of the test guideline

38 To fulfil the information requirement, a study must comply with OECD TG 471 (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) at least 5 doses are evaluated, in each test condition;

b) triplicate plating is used at each dose level;

c) a concurrent negative control is included in each assay and the number of revertant colonies per plate for the concurrent negative control is inside the historical control range of the laboratory;

d) the mean number of revertant colonies per plate is reported for the treated doses and the controls;

e) negative results are confirmed in a repeat experiment with modification of study parameters to extend the range of conditions assessed, or a justification why confirmation of negative results is not considered necessary is provided.

39 In the provided study:

a) the report states "*Precipitates were observed in all concentrations with and without S9 mix*". Therefore, it is not possible to know if 5 doses were evaluated in absence and in presence of metabolic activation;

b) triplicate plating was not used at each dose level;

c) a concurrent negative control was not included in the study;

d) the mean number of revertant colonies per plate for the treated doses and the controls was not reported;

e) no repeat experiment was performed to confirm the negative results and no justification was provided.

40 The information provided does not cover the specification(s) required by the OECD TG 471.

41 Therefore, the information requirement is not fulfilled.

Reasons related to the information under Annex VIII of REACH

3. *In vitro* micronucleus study

42 An *in vitro* mammalian chromosomal aberration study or an *in vitro* mammalian micronucleus study is an information requirement under Annex VIII, Section 8.4.2.

3.1. Information provided

43 You have provided an *in vitro* cytogenicity study in mammalian cells (2011) with the Substance.

3.2. Assessment of the information provided

3.2.1. The provided study does not meet the specifications of the test guideline

44 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. The study must comply with the OECD TG 473 or the OECD TG 487, respectively (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) at least 3 concentrations are evaluated, in absence and in presence of metabolic activation;

b) at least 300 well-spread metaphases are scored per concentration;

c) the positive controls induce responses compatible with those generated in the historical positive control database;

d) the positive controls produce statistically significant increase compared with the negative control;

e) the negative control data is ideally within the 95% control limits of the distribution of the laboratory's historical negative control database;

f) data on the cytotoxicity and the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures is reported.

45 In the provided study:

a) 1 concentration (i.e., less than 3 concentrations) were evaluated in absence and in presence of metabolic activation;

b) the number of metaphases (i.e., less than 300 metaphases) that were scored per concentration was not reported;

c) the historical positive control database was not reported;

d) the positive control did not produce a statistically significant increase in the induced response when compared with the concurrent negative control;

e) the historical control range of the laboratory was not reported;

f) data on the cytotoxicity and/or the frequency of cells with structural chromosomal aberration(s) for the treated and control cultures were not reported;

46 The information provided does not cover the specifications required by the OECD TG 473.

47 Therefore, the information requirement is not fulfilled.

3.3. Study design

48 According to the Guidance on IR & CSA, Section R.7.7.6.3., either the in vitro mammalian chromosomal aberration ("CA") test (test method OECD TG 473) or the in vitro mammalian cell micronucleus ("MN") test (test method OECD TG 487) can be used to investigate chromosomal aberrations in vitro. However, while the MN test detects both structural chromosomal aberrations (clastogenicity) and numerical chromosomal aberrations (aneuploidy), the CA test detects only clastogenicity, as OECD TG 473 is not designed to measure aneuploidy (see OECD TG 473, paragraph 2). Therefore, you must perform the MN test (test method OECD TG 487), as it enables a more comprehensive investigation of the chromosome damaging potential in vitro. Moreover, in order to demonstrate the ability of the study to identify clastogens and aneugens, you must include two concurrent positive controls, one known clastogen and one known aneugen [1] (OECD TG 487, paragraphs 33 to 35).

3.3.1. Assessment of aneugenicity potential

49 If the result of the MN test is positive, i.e. your Substance induces an increase in the frequency of micronuclei, you must assess the aneugenic potential of the Substance.

50 In line with the OECD TG 487 (paragraph 4), you should use one of the centromere labelling or hybridisation procedures to determine whether the increase in the number of micronuclei is the result of clastogenic events (i.e. micronuclei contain chromosome fragment(s)) and/or aneugenic events (i.e. micronuclei contain whole chromosome(s)).

[1] According to the TG 487 (2016) "At the present time, no aneugens are known that require metabolic activation for their genotoxic activity" (paragraph 34).

4. *In vitro* gene mutation study in mammalian cells

51 An *in vitro* gene mutation study in mammalian cells is an information requirement under Annex VIII, Section 8.4.3., in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

4.1. Triggering of the information requirement

52 Your dossier contains data for an *in vitro* gene mutation study in bacteria, and data for an *in vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study.

53 The information for the *in vitro* gene mutation study in bacteria and for the *in vitro* cytogenicity study in mammalian cells provided in the dossier are rejected for the reasons provided in requests 0 and 3.

54 The result of the requests for an *in vitro* gene mutation study in bacteria and for an *in vitro* micronucleus study will determine whether the present requirement for an *in vitro* mammalian cell gene mutation study in accordance with Annex VIII, Section 8.4.3. is triggered.

55 Consequently, you are required to provide information for this information requirement, if the *in vitro* gene mutation study in bacteria and the *in vitro* micronucleus study provide a negative result.

4.2. Information provided

56 You have adapted this information requirement by using Annex VIII, Section 8.4., Column 2. To support the adaptation, you have provided the following:

(i) information on a group of substances derived from the OECD QSAR Toolbox version 3.3 for *in vivo* genetic toxicity.

4.3. Assessment of the information provided

4.3.1. The provided adaptation does not meet the criteria of Annex VIII, Section 8.4.2., Column 2

4.3.1.1. Read-across adaptation rejected

57 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.

58 On this basis, your adaptation under Annex VIII, Section 8.4.2., Column 2 is rejected.

59 Therefore, the information requirement is not fulfilled.

4.4. Study design

60 To fulfil the information requirement for the Substance, either the *in vitro* mammalian cell gene mutation tests using the hprt and xprt genes (OECD TG 476) or the thymidine kinase gene (OECD TG 490) are considered suitable.

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

61 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.

5.1. Information provided

62 You have provided a sub-acute toxicity study (2011) with the Substance.

5.2. Assessment of the information provided

5.2.1. The provided study does not meet the specifications of the test guideline

63 To fulfil the information requirement, a study must comply with the OECD TG 407 (Article 13(3) of REACH). Therefore, the following specifications must be met:

a) body weight is measured at least weekly;

b) clinical signs (nature, severity, and duration) are observed daily and functional observations (i.e. sensory activity, grip strength and motor activity) are made during the fourth exposure week;

c) haematological and clinical biochemistry tests are performed as specified in paragraphs 32-39 of OECD TG 407;

d) terminal organ and body weights are measured;

e) gross pathological examinations, including incidence and severity, as specified in paragraphs 40-46 of OECD TG 407 are performed.

f) full histopathology, including incidence and severity, is performed as specified in paragraphs 47-49 of OECD TG 407.

64 In study (i):

g) body weights were not assessed at least weekly;

h) clinical signs and functional aspects were not assessed: nature, severity and duration;

i) haematology and clinical biochemistry were not performed: incidence and severity with relevant base-line values;

j) terminal organ weights and organ/body weight ratios were not recorded;

k) gross pathology aspects were not covered;

l) the following histopathology items were not studied (incidence and severity): brain, spinal cord, eye, stomach, thyroid, trachea, lungs, gonads, accessory sex organs, vagina, urinary bladder, lymph nodes, peripheral nerve, skeletal muscle and bone, with bone marrow.

65 The information provided does not cover the specification(s) required by the OECD TG 407.

66 Therefore, the information requirement is not fulfilled.

5.3. Study design

67 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.).

68 The study design is addressed in request 6.

6. Screening study for reproductive/developmental toxicity

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

6.1. Information provided

70 You have provided information on a group of substances derived from the OECD QSAR Toolbox version 3.3 for toxicity to reproduction.

6.2. Assessment of the information provided

6.2.1. Read-across adaptation rejected

71 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.

72 Therefore, the information requirement is not fulfilled.

6.3. Study design

73 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.

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

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

76 Since the adopted decision no longer contains a request for a sub-chronic (90 days) study (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.

7. Long-term toxicity testing on fish

77 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.

7.1. Triggering of the information requirement

78 In the provided key study for short-term fish toxicity OECD TG 203 (2005), the saturation concentration of the Substance in water was determined to be 0.0274 mg/L.

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

7.2. Information provided

80 You have provided the following information in your registration dossier:

(i) A waiver stating: '*According to EC 1907/2006, Annex IX, Column 2, long term toxicity testing shall be proposed if the chemical safety assessment according to Annex I indicates the need to investigate further the effects on aquatic organisms. Amides, C16-C18 (even), N, N'-ethylenebis is highly insoluble in water, and therefore its bioavailability through this exposure route is limited. Moreover, the substance did not exert toxicity to any of the aquatic organisms used in the experimental studies available (acute toxicity to invertebrates, algae, microorganisms, and acute toxicity to fish), included Daphnia after 21 days of exposure (long term study). Since there is no indication that fish sensitivity would be greater than that of Daphnia, similar results for long term fish studies can be expected. Therefore, and in order to preserve animal welfare, further testing for this endpoint it is not considered necessary'*

(ii) A QSAR estimation for long-term fish toxicity using Episuite v4.11 (ECOSAR v1.11) QSAR class amides: ChV (NOEC) (30 d): 0.00102 µg/L test mat. (nominal) based on: Mortality

7.3. Assessment of the information provided

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

81 Annex IX, Section 9.1., Column 2 is not a basis for omitting information on long-term toxicity to fish referred to under Column 1, Section 9.1.6.

82 Your adaptation is therefore rejected.

83 Furthermore, minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under the general rules of Annex XI.

7.3.2. The provide QSAR prediction is not reliable

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

1. The prediction needs to be derived from a scientifically valid model

2. The substance must fall within the applicability domain of the model
3. Results need to be adequate for the purpose of risk assessment or classification and labelling, and
4. Adequate and reliable documentation of the method must be provided.

85 With regard to these conditions, we have identified the following issues:

7.3.2.1. Inadequate documentation of the prediction (QPRF)

86 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:

- 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.

87 You provided the following information about the prediction: The ECOSAR amide model prediction for long term fish toxicity for the Substance of ChV (NOEC) (30 d): 0.00102 µg/L test mat. (nominal) based on the following calculated input values for Log Kow: 13.98 (EPISuite Kowwin v1.68 Estimate) and water solubility: 2.049E-010 (mg/L, EPISuite WSKowwin v1.43 Estimate).

88 The information you provided about the prediction lacks the following elements:

- You do not provide any information or justification to establish a valid relationship between the modelled substance and the defined applicability domain. The training set of the ECOSAR amide ChV fish model covers the Log Kow range 0.5 to 4.7. The Substance has a Log Kow 13.98 which is not covered by the Log Kow range of the amide fish ChV model in ECOSAR.
- You have not provided any additional information on structurally similar analogue substances to establish that the model provides accurate predictions for this Substance.

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

7.3.2.2. The substance is outside the applicability domain of the model

90 Under Guidance on IRs and CSA R.6.1.5.3., a prediction is within the applicability domain of the model, when, among others, the substance falls within the descriptor, structural, mechanistic and metabolic domains.

91 You report in registration dossier that the Substance has a Log Kow 13.98

92 The training set of the ECOSAR amide ChV fish model includes 7 substances covering the Log Kow range from 0.5 to 4.7. In addition, the limit for Log Kow for the applicability of the ECOSAR ChV model is 8.0. The substance has a Log Kow of 13.98 which exceeds the Log Kow range covered by the amide model, and the overall maximum Log Kow for the ECOSAR ChV model. The Substance is therefore outside the structural applicability domain of the model.

93 Therefore, the information requirement is not fulfilled.

7.4. Study design

94 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.).

95 The Substance is difficult to test due to its low water solubility (0.0274 mg/L) and adsorptive properties (log K_{ow} 13.98). OECD TG 210 specifies that, for difficult to test substances, you must 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.

96 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).

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

- 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 22 February 2023.

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

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

In your comments you agreed to the draft decision. ECHA took your comments into account 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.

As a result of one or more changes of registration tonnage band or registration type, the requests for

- Sub-chronic toxicity study (90 days; Annex IX, Section 8.6.2.; test method: OECD TG 408)
- Pre-natal developmental toxicity study in one species (Annex IX, Section 8.7.2.; test method: OECD TG 414)
- Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: EU C.47./OECD TG 210)

were removed from the decision. Consequently, an editorial change was made to the request 5 to remove an obsolete alternative.

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]

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/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.

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).