~~Confidential~~

Helsinki, 19 August 2021

Addressees
Registrant(s) of JS_94441-92-6 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
07/01/2020

Registered substance subject to this decision ("the Substance")
Substance name: Sodium N-(2-carboxyethyl)-N-(2-ethylhexyl)-β-alaninate
EC number: 305-318-6
CAS number: 94441-92-6

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 the deadline of ***24 November 2023***.

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

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

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

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

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

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

2. 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)

3. Long-term toxicity testing on fish (Annex IX, Section 9.1.6.; test method: OECD TG 210)

Reasons for the request(s) are explained in the following appendices:

- Appendix entitled "Reasons common to several requests";
- Appendices entitled "Reasons to request information required under Annexes VIII to IX of REACH", respectively.

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- 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;

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 testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

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 Christel Schilliger-Musset, Director of Hazard Assessment

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

Appendix on Reasons common to several requests

1. Assessment of your read-across approach under Annex XI, Section 1.5.

You seek to adapt the following standard information requirements by applying (a) read-across approach(es) in accordance with Annex XI, Section 1.5:

- 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.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

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 appendices.

Grouping of substances and read-across approach

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

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance R.6. and related documents[2,3].

A. Scope of the grouping

i. Description of the grouping

You have not provided any separate read-across justification document in your dossier.
ECHA understands that you define the the structural basis for the grouping as metabolites of primary alkylamines ("*The similarity in findings with the work on primary amines further justifies read-across to these potential metabolites*"). ECHA understands that this is the applicability domain of the grouping and will assess your predictions on this basis.

B. Predictions for toxicological properties

You have provided the following reasoning for the prediction of toxicological properties: In your dossier you have not provided any read-across justification document. However, under the endpoint summary for repeated dose toxicity you provided the following statement "*Examination of data on various primary alkylamines show little difference in repeat toxicity effects, including reproduction. Read-across is considered valid as the results are consistent with the findings in the more recent 28 days study (key study); this study show more adverse effects and is therefore considered a suitable surrogate for the reporting of reproductive effects. The similarity in findings with the work on primary amines further justifies read-across to these potential metabolites. This is reviewed in the assessment report attached in Section 13".*

[2] Read-Across Assessment Framework (RAAF). 2017 (March) ECHA, Helsinki. 60 pp. Available online: Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across)
[3] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs. 2017 (March) ECHA, Helsinki. 40 pp. Available online: https://doi.org/10.2823/794394

ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. The properties of your Substance are predicted based on an identified trend within the group.

You intend to predict the properties for the category members from information obtained from the following source substances:

- β-Alanine, N-(2-carboxyethyl)-, N-coco alkyl derivs., disodium salts (EC 290-476-8),
- Disodium N-(2-carboxyethyl)-N-dodecyl-â-alaninate (EC 222-899-0) and
- Ethyl N-acetyl-N-butyl-â-alaninate (EC 257-835-0)

and the Substance as target substance.

ECHA notes the following shortcomings with regards to predictions of toxicological properties.

Read-across hypothesis

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled to apply grouping and read-across. 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 (read-across approach).

A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the substances[4]. It should explain why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern.

ECHA understands that your read-across hypothesis is that the structural similarity and toxicological properties of the source substance(s) and your Substance is a sufficient basis for predicting the properties of your Substance.

While structural similarity is a prerequisite for applying the grouping and read-across approach, it does not necessarily lead to predictable or similar human health properties. You have not provided a well-founded hypothesis to establish a reliable prediction for a toxicological property, based on recognition of the structural similarities and differences between the source substance(s) and your Substance.

Supporting information

Annex XI, Section 1.5 of the REACH Regulation states that "*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*". For this purpose "*it is important to provide supporting information to strengthen the rationale for the read-across*"[5]. The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on other category members.

[4] *Guidance on information requirements and chemical safety assessment*, Chapter R.6: QSARs and grouping of chemicals.
[5] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals, Section R.6.2.2.1.f

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

As indicated above, your read-across hypothesis is based on the assumption that the structurally similar category members cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the category members is necessary to confirm that both substance cause the same type of effects. Such information can be obtained, for example, from bridging studies of comparable design and duration for the category members.

You consider that "*Examination of data on various primary alkylamines show little difference in repeat toxicity effects, including reproduction".* However, your dossier does not contain any bridging information on the Substance for reproductive or developmental effects. The data set reported in the technical dossier does not include relevant, reliable and adequate information for the category members to support your read-across hypothesis.

In the absence of such information, you have not established that the category members are likely to have similar properties. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

In your comments on the initial draft decision you explain that you will update your read-across justification. In your comments you did not provide further details or supporting documentation. On this basis, the information in your comments is not sufficient for ECHA to make an assessment. Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation)."

C. Conclusions on the read-across approach

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

2. Assessment of your weight of evidence adaptation under Annex XI, Section 1.2.

You have adapted the following standard information requirements by applying weight of evidence (WoE) adaptation in accordance with Annex XI, Section 1.2:

- Screening for reproductive/developmental toxicity study (Annex VIII, Section 8.7.1)
- Sub-chronic toxicity study (Annex IX, Section 8.6.2)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2).

Your weight of evidence adaptation raises the same decifiencies irrespective of the information requirement for which it is invoked. Accordingly, ECHA addressed these deficiencies in the present Appendix, before assessing the specific standard information requirements in the following appendices.

Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory information requirement. Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

However, for each relevant information requirement, you have 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.

In spite of this critical deficiency, ECHA has nevertheless assessed the validity of your adaptation. Your weight of evidence approach has deficiencies that are common to all information requirements under consideration and also deficiencies that are specific for these information requirements individually. The common deficiencies are set out here, while the specific ones are set out under the information requirement concerned in the Appendices below.

The issue identified below is essential for all the information requirements in which you invoked a weight of evidence.

In your comments on the initial draft decision you explain that you will update your weight of evidence justification. In your comments you did not provide further details or supporting documentation. On this basis, the information in your comments is not sufficient for ECHA to make an assessment. Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation)."

Reliability of the read across approach

Section 1. of the present Appendix identifies deficiencies of the grouping and read across approach used in your dossier. These findings apply equally to the sources of information relating to analogue substances submitted under your weight of evidence adaptations.

Additional issues related to weight of evidence are addressed under the corresponding endpoints.

Appendix A: Reasons to request information required under Annex VIII of REACH

1. In vitro gene mutation study in mammalian cells

An *in vitro* gene mutation study in mammalian cells is an information requirement under Annex VIII to REACH (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.

i. Triggering of the study

Your dossier contains negative results for both an Ames test and an *in vitro* cytogenicity study. Therefore, the information requirement is triggered.

ii. Assessment of information provided

You have provided a key study in your dossier:

(i) In vitro mammalian cell gene mutation study with the Substance (2013)

Furthermore, you have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. You provided one study:

(ii) In vitro mammalian cell gene mutation study with an analogue substance (2013)

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

To fulfil the information requirement, the *in vitro* gene mutation study on mammalian cells has to meet the requirements of OECD TG 476 or OECD TG 490[6]. The key parameter(s) of these test guidelines include:

a) At least 4 concentrations must be evaluated, in each test condition.
b) One positive control must be included in the study. The positive control substance must produce a statistically significant increase in the response compared with the concurrent negative control.
c) The response for the concurrent negative control must be inside the historical control range of the laboratory.
d) Data on the cytotoxicity and the mutation frequency for the treated and control cultures must be reported.

The reported data for the study (i) you have provided do not include:

a) the evaluation of at least 4 concentrations in each test condition.
b) one positive control that produced a statistically significant increase in the number of revertant colonies per plate compared with the concurrent negative control.
c) a negative control with a response inside the historical control range of the laboratory.
d) data on the cytotoxicity and the mutation frequency for the treated and control cultures.

In addition, ECHA notes that in your dossier you have not included details on the study design and results, and you explain: *"Preliminary results from a GLP mouse lymphoma assay (OECD 476) show no mutagenicity with or without S9 mix in concentrations up to 5000 µg/ml, or to a cytotoxicity level of 81%. The dossier will be updated as soon as the test report is available".*

Thus, the information (i) provided does not cover key parameters required by OECD TG 476/490.

[6] ECHA Guidance R.7a, Table R.7.7–2, p.557

Furthermore, as explained in the Appendix on Reasons common to several requests, your adaptation under Annex XI, Section 1.5. is rejected.

Therefore, the information requirement is not fulfilled.

In your comments on the initial draft decision you explain that you will update your read-across and weight of evidence adaptations. Furthermore, you state that "in the event that robust data cannot be provided, a new study will be commissioned". In your comments you did not provide further details or supporting documentation. On this basis, the information in your comments is not sufficient for ECHA to make an assessment. Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation)."

Study design

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

2. Screening for reproductive/developmental toxicity

A Screening for reproductive/developmental toxicity study (test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) is a standard information requirement under Annex VIII to REACH, if there is no evidence from analogue substances, QSAR or *in vitro* methods that the Substance may be a developmental toxicant. There is no information available in your dossier indicating that your Substance may be a developmental toxicant.

You have provided adaptations under under Annex XI, Section 1.2. of REACH (weight of evidence) and under Annex XI, Section 1.5. of REACH (grouping and read-across). In support of your adaptations, you have provided the following sources of information:

(i) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422, 2009) with an analogue substance (EC 222-899-0)
(ii) Two-generation study (OECD TG 416, 1999) with an analogue substance (EC 257-835-0).

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

Read-across

As explained in the Appendix on Reasons common to several requests (section 1), your adaptation under Annex XI, Section 1.5. is rejected.

Weight of evidence

As explained under Appendix on Reasons common to several requests (section 2), the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

To fulfil this information requirement, normally a study performed according to EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be provided. OECD TGs 421/422 require to investigate the following key elements: 1) sexual function and fertility, 2) toxicity to offspring, and 3) systemic toxicity.

The studies you submitted provide relevant information on sexual function and fertility, toxicity to offspring, and systemic toxicity.

However, the reliability of these sources of information is significantly affected by the deficiencies identified under Appendix on Reasons common to several requests (section 2).

Therefore, it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 421/422 study. Thus your adaptation is rejected.

Conclusion

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

In your comments on the initial draft decision you explain that you will update your read-across and weight of evidence adaptations. Furthermore, you state that "in the event that robust data cannot be provided, a new study will be commissioned but only as a last resort in line with our obligations under the 3R's framework".

Information on study design

A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats with oral[7] administration of the Substance.

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

Appendix B: Reasons to request information required under Annex IX of REACH

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

A Sub-chronic toxicity study (90 day) is a standard information requirement under Annex IX to REACH.

You have provided in your dossier:

a) (i) Sub-acute toxicity study (28 days; OECD TG 407, 2012) with the Substance.

b) Adaptations under Annex XI, Section 1.2. of REACH (weight of evidence) and under Annex XI, Section 1.5. of REACH (grouping and read-across). In support of your adaptations, you have provided the following sources of information:
(ii) Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422, 2009) with an analogue substance (EC 222-899-0)
(iii) Two-generation study (OECD TG 416, 1999) with an analogue substance (EC 257-835-0).

c) A data waiver: "*The arguments for waiving such a test are: 1) Due to the results from the available tests, Sodium N-(2-carboxyethyl)-N-(2-ethylhexyl)-β-alaninate, CAS No 94441-92-6, does not have to be classified as dangerous in accordance with Directive 67/548/EEC and has no obligatory labeling requirement on any endpoint. As stated in Article 14 of the REACH legislation, the chemical safety assessment on a non-classified substance does not need to include an exposure assessment nor risk characterization. It is therefore not needed to perform any 90-day oral toxicity study in order to refine any DNEL derivations. 2) According to OECD guideline 408 at least 20 animals (10 females and 10 males) are to be used at each dose level, and at least three dose groups and a concurrent control shall be used in the 90-day oral toxicity study, resulting in the use of 80 animals in total. Based on animal welfare grounds, it is not considered ethically justified to perform a test using 80 animals to perform an additional test on a non-toxic substance. The possibility to perform a limit test is given in the guidance with one dose level of at least 1000 mg/kg bw for substances with low toxicity. The lack of any effects at 1000 mg/kg bw in the 28 day oral toxicity study makes it implausible to expect effects in a prolonged study, since a LOAEL could not be identified in the already performed repeated dose study. A 90-day oral toxicity study is therefore not expected to add any further relevant knowledge on this endpoint. 3) In Directive 67/548/EEC, the EU CLP (GHS) criteria for classification for Specific Target Organ Toxicity (STOT) are given based on data from a 90 day study. For classifying a substance according to STOT Category 2, the range for such effects is 10-<100 mg/kg/day. Performing a limited 90-day test on Sodium N-(2-carboxyethyl)-N-(2-ethylhexyl)-β-alaninate, CAS No 94441-92-6, with the proposed dose level of 1000 mg/kg bw would therefore not provide any additional data for classification and labeling purposes. Considering the above mentioned arguments, it is not regarded relevant from a scientific point, nor justified on animal welfare grounds, to perform a 90 Day Toxicity, oral (gavage) in rat according to OECD guideline 408.*

We have assessed this information and identified the following issues:

a) 28-day study

To be considered compliant and enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL),

a study has to meet the requirements of OECD TG 408. The key parameter(s) of this test guideline include, among others

- At least 10 female and 10 male animals should be used at each dose level (including control group)
- Dosing of the Substance daily for a period of 90 days until the scheduled termination of the study

The study you have provided was conducted with less than 10 animals per sex per test dose group. The statistical power of the information provided is not sufficient because it does not fulfil the criterion of 20 animals (10 males + 10 females) for each test group set in OECD TG 408. Furthermore, the study you have provided does not have the required exposure duration of 90 days, because you indicated an exposure duration of 28 days.

Therefore, the information you provided does not fulfil the information requirement.

b) Annex XI adaptations

Read-across

As explained in the Appendix on Reasons common to several requests (section 1), your adaptation under Annex XI, Section 1.5. is rejected.

Weight of evidence

As explained under Appendix on Reasons common to several requests (section 2), the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

To fulfil this information requirement, normally a study performed according to OECD TG 408 must be provided. OECD TG 408 requires to investigate the following key elements: 1) in-life observations, 2) blood chemistry, 3) organ and tissue toxicity. Information should address effects on the following physiological systems: circulatory system, digestive/excretory system, endocrine system, immune system, integumentary system, musculoskeletal system, nervous system, renal/urinary system, reproductive system, and respiratory system

Sources of information (ii-iii), provide information on these key elements. The sources of information (ii-iii) provide relevant information on in-life observations and organ and tissue toxicity. Furthermore, the source of information (ii) provides relevant information on blood chemistry.

These sources of information, however, have the following deficiencies affecting their reliability.

OECD TG 408 include the following key parameters: dosing of at least 10 non-pregnant female and 10 male animals per dose group daily for a period of 90 days until the scheduled termination of the study, clinical observations, ophthalmological examination, sensory reactivity to various stimuli and functional observations of the animals, recording of body weight, hematology, clinical biochemistry, and pathology of sexual (male and female) organs, full detailed gross necropsy and subsequent histopathology.

The source of information (ii) does not have the required exposure duration of 90 days, because the exposure duration of the screening test is approximately 63 days (for females)

and 28 days (for males). Furthermore the organ weight and histopathological investigations in OECD TG 422 are only conducted using only five animals per sex per group.

The source of information (iii) does not inform on, or it is unclear whether investigations were made on ophthalmological examination, functional observations of the animals, hematology, clinical biochemistry, full detailed gross necropsy and subsequent histopathology.

In addition, the reliability of sources of information (ii) and (iii) are significantly affected by the deficiency identified and explained under Appendix on Reasons common to several requests (section 2).

Therefore, the studies you submitted provide only partly relevant information on sub-chronic toxicity and their reliability is significantly affected.

It is not possible to conclude, based on any of the new sources of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in OECD TG 408. Therefore your adaptation under Annex XI, Section 1.2, is rejected.

c) Data waiver

You did not provide any legal basis for your waiver and it is not clear whether it is in accordance neither with the provisions of Annex XI nor with Annex IX, Section 8.6.2, Column 2. Therefore it cannot be further evaluated.

Conclusion

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

In your comments on the initial draft decision you explain that you will update your read-across and weight of evidence adaptations. Furthermore, you state that "in the event that robust data cannot be provided, a new study will be commissioned but only as a last resort in line with our obligations under the 3R's framework". In your comments you did not provide further details or supporting documentation. On this basis, the information in your comments is not sufficient for ECHA to make an assessment. Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation)."

Information on the design of the study to be performed

Referring to the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity, because the substance is a solid (paste).

Therefore the sub-chronic toxicity study must be performed according to the OECD TG 408, in rats and with oral administration of the Substance

2. Pre-natal developmental toxicity study in one species

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX to REACH.

You have provided adaptations under Annex XI, Section 1.2. of REACH (weight of evidence) and under Annex XI, Section 1.5. of REACH (grouping and read-across). In support of your

adaptations, you have provided two pre-natal developmental toxicity studies (similar to OECD TG 414, 1999) in rabbits performed with an analogue substance (EC 257-835-0).

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

Read-across

As explained in the Appendix on Reasons common to several requests (section 1), your adaptation under Annex XI, Section 1.5. is rejected.

Weight of evidence

As explained under Appendix on Reasons common to several requests (section 2), the weight of evidence adaptation must fulfil the information requirement based on relevant and reliable sources of information. These sources of information must provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Relevant information that can be used to support weight of evidence adaptation for information requirement of Section 8.7.2 at Annex IX includes similar information that is produced by the OECD TG 414 on one species. The following key elements are covered: 1) prenatal developmental toxicity, 2) maternal toxicity, and 3) maintenance of pregnancy.

The studies you provided provide relevant information on prenatal developmental toxicity, maternal toxicity, and maintenance of pregnancy.

However, the reliability of the sources of information is significantly affected by the deficiency identified and explained under Appendix on Reasons common to several requests (section 2).

Therefore, the information provides information on pre-natal developmental toxicity but its reliability is significantly affected.

It is not possible to conclude, based on any of the new sources of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in OECD TG 414. Therefore your adaptation under Annex XI, Section 1.2, is rejected.

Conclusion

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

In your comments on the initial draft decision you explain that you will update your read-across and weight of evidence adaptations. Furthermore, you state that "in the event that robust data cannot be provided, a new study will be commissioned but only as a last resort in line with our obligations under the 3R's framework". In your comments you did not provide further details or supporting documentation. On this basis, the information in your comments is not sufficient for ECHA to make an assessment. Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation)."

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[8] administration of the Substance.

[8] ECHA Guidance R.7a, Section R.7.6.2.3.2.

3. Long-term toxicity testing on fish

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

You have provided the following information:

i. a justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2. In support of your adaptation, you provided the following justification *'According to Annex IX, 9.1.6 to the Reach Regulation long-term toxicity testing with fish shall be proposed only if the CSA indicates the need to investigate further the effects on aquatic organisms. However, the CSA does not indicate the need for further testing of vertebrates. Moreover, the low bioaccumulative potential does not trigger the need for long-term testing. Therefore long-term toxicity testing with fish is waived in order to avoid unnecessary vertebrate testing.'*

We have assessed this information and identified the following issues:

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

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

Your justification in respect of bioaccumulation and animal welfare considerations to omit this information does not refer to any legal ground for adaptation under Annex XI to REACH.

Therefore, you have not demonstrated that this information can be omitted. Low bioaccumulative potential or minimisation of vertebrate animal testing is not on its own a legal ground for adaptation under the general rules of Annex XI.

Your adaptation is therefore rejected.

On this basis, the information requirement is not fulfilled.

In your comments on the initial draft decision you explain that you will update your read-across and weight of evidence adaptations. Furthermore, you state that "in the event that robust data cannot be provided, a new study will be commissioned but only as a last resort in line with our obligations under the 3R's framework". In your comments you did not provide further details or supporting documentation. On this basis, the information in your comments is not sufficient for ECHA to make an assessment. Please note that this decision does not take into account updates of the registration dossiers after the date on which you were notified of the draft decision according to Article 50(1) of REACH (see section 5.4. of ECHA's Practical Guide "How to act in Dossier Evaluation)."

Study design

To fulfil the information requirement for the Substance, the Fish, Early-life Stage Toxicity Test (test method OECD TG 210) is the most appropriate (ECHA Guidance R.7.8.2.).

The Substance is difficult to test due to the surface active properties and ionisable properties (surface tension= 52 mN/m, pKas are 4.51 and 8.17). 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.

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).

Appendix C: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. 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[9].

B. 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:

a) the variation in compositions reported by all members of the joint submission,
b) the boundary composition(s) of the Substance,
c) 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

a) 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.
b) 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[10].

[9] https://echa.europa.eu/practical-guides
[10] https://echa.europa.eu/manuals

Appendix D: General recommendations when conducting and reporting new tests for REACH purposes

A. Environmental testing for substances containing multiple constituents

Your Substance contains multiple constituents and, as indicated in ECHA Guidance R.11 (Section R.11.4.2.2), you are advised to consider the following approaches for persistency, bioaccumulation and aquatic toxicity testing:

- the "known constituents approach" (by assessing specific constituents), or
- the "fraction/block approach, (performed on the basis of fractions/blocks of constituents), or
- the "whole substance approach", or
- various combinations of the approaches described above

Selection of the appropriate approach must take into account the possibility to characterise the Substance (i.e. knowledge of its constituents and/or fractions and any differences in their properties) and the possibility to isolate or synthesize its relevant constituents and/or fractions.

Appendix E: 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 12 August 2020.

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).

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 F: List of references - ECHA Guidance[11] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[12]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[13]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[14]

[11] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[12] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[13] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[14] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

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

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

Appendix G: Addressees of this decision and their corresponding information requirements

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[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.