~~Confidential~~

Helsinki, 08 September 2021

Addressees
Registrants of JS_308-072-8 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
26/05/2013

Registered substance subject to this decision ("the Substance")
Substance name: Butanedioic acid, sulfo-, 4-[2-[(2-hydroxyethyl)amino]ethyl] ester, N-C18-unsatd. acyl derivs., disodium salts
EC number: 308-072-8
CAS number: 97862-28-7

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 ***16 December 2024***.

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

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

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

2. Ready biodegradability (Annex VII, Section 9.2.1.1.; test method: OECD TG 301B/C/D/F or OECD TG 310)

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

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

2. If negative results are obtained in test performed for the information requirement of Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. then: In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490)

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

4. 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

C. Information required from 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)

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 VII 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 information requirements for the following standard information requirements by grouping substances in the category and applying a read-across approach in accordance with Annex XI, Section 1.5:

- In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)
- In vitro cytogenicity study in mammalian cells or in vitro micronucleus study (Annex VIII, Section 8.4.2.)
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)
- Sub-chronic toxicity study (90-day), (Annex IX, Section 8.6.2.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)
- Ready Biodegradability study (Annex VII, Section 9.2.1.1)

ECHA has considered the scientific and regulatory validity of your grouping and read-across approach 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 (addressed under 'Scope of the grouping'). Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (addressed under 'Assessment of prediction(s)').

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

A. **Scope of the grouping**

In your registration dossier you have formed a group (category) of Sulfosuccinates. You have provided two justification documents as separate attachments in IUCLID, section 13: a read-across justification document for the group of sulfosuccinates named "[redacted] hereafter "category justification document" and a justification document for the N2-subgroup "[redacted], hereafter "justification document".

In the category justification document you provide the general structures of the sulfosuccinates and make a general characterization of their (eco)toxicity. You conclude that "[…] *in total there are 5 subgroups considered for the detailed read across argumentation. Within the subgroups, the substances may be ordered according to their C-Chain-Lengt*".

In the justification document you have specifically addressed the N2-subgroup, providing the reasoning for grouping and read-across between the members of this subgroup. You have also provided a data matrix on physico-chemical and (eco)toxicological properties of the substances.

In the justification document you list the substances below as members of the N2-subgroup:

1. C11'-MEA: Disodium 4-[2-[(1-oxoundec-10-enyl)amino]ethyl] 2-sulphonatosuccinate (EC No. 247-873-6);
2. C12-C18/C18'-MEA: Butanedioic acid, 2(or 3)-sulfo-, 4-[2-[(1-oxo(C12-C18(even numbered) and C18 unsaturated)alkyl))amino]ethyl]esters, disodium salts (EC No. 939-637-2), hereafter 'source substance [1]';
3. C12-MEA: Butanedioic acid, 2(or 3)-sulfo-, 4-[2-[(1-oxododecyl)amino]ethyl] ester,disodium salt (EC´No. 939-648-2);
4. C18'-MiPA: Butanedioic acid, 2-sulfo-, 4-[1-methyl-2-[(1-oxo-9-octadecen-1-yl)amino]ethyl] ester, sodium salt (EC No. 267-199-6; CAS: 67815-88-7)
5. C18'-OH-MEA: Reaction products of ricinoleic acid with 2-aminoethanol and maleic acid and sodium hydrogensulfite (EC No. 939-654-5), hereafter 'source substance [2]'; and
6. C18'-DEA: Butanedioic acid, sulfo-, 4-[2-[(2-hydroxyethyl)amino]ethyl] ester, N-C18-unsatd. acyl derivs., disodium salts (EC No. 308-072-8, hereafter 'the Substance'.

ECHA understands that this is the applicability domain of the grouping and your predictions are assessed on this basis.

ECHA has analysed the provided information and has identified the following issue(s):

You have provided the following reasoning for the sub-grouping: *"All members of the N2-sulfosuccinate subgroup, are monoesters of sulfosuccinic acid. Beside the sulfosuccinate group they do not contain other bonds than C-C , C-N, C-O and C-H. The alkyl rests may be linear, saturated or unsaturated".* Further, you list the following characteristics of the subgroup:

- *"similarities in the chemical process*
- *functional groups*
- *general composition"*

You defined the applicability domain of the subgroup as follows: "*The subgroup can only be applied to those substances that share all the same functional groups and for which the alkyl group comprises a C-chain length from C10 to C22 (even-numbered, C18: saturated or unsaturated or double unsaturated, C20 and C22 unsaturated or C18-OH unsaturated). The main C-chain distribution is C12 and C18 of all members of this subgroup"*.

ECHA understands that this is the applicability domain of the grouping and your predictions are assessed on this basis.

B. Predictions for (eco)toxicological properties

I. Prediction within the subgroup N2

You have provided the following reasoning for the prediction of toxicological properties:

"*The subgroup […] is built on the following characteristics:*
- similarities in the chemical process
- similar functional groups
- similar general composition […]
The assumption that the properties of the subgroup members are similar can be shown by a comparison of the physical-chemical and toxicological data […]"

You have provided the following hypothesis for the prediction of toxicological properties: "*no trend with the subgroup could be observed, which is primarily explainable by the general low toxicity in the whole subgroup*". In order to support your hypothesis, you further referred to similarities in the acute toxicity, skin irritation, eye irritation, skin sensitisation properties of the category members.

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. Thus, the toxicological properties of the Substance are predicted to be quantitatively equal to those of the source substances.

ECHA has analysed the provided information and has identified the following issues:

(i) *Missing relevant supporting information*

According to the ECHA Guidance[2] "*it is important to provide supporting information to strengthen the rationale for the read-across approach. Thus, in addition to the property/endpoint being read-across, it is also useful to show that additional properties, relevant to the endpoint, are also (qualitatively or quantitatively) similar between the source and target chemicals*".

In order to support your claim that the substances included in the sub-group have similar properties for the endpoints under consideration in the read-across approach, you refer to the acute toxicity, skin irritation, eye irritation, skin sensitisation properties of the sub-group members.

Whilst all the supporting information you have provided suggests that the substances may have similar properties for acute toxicity, skin and eye irritation, and skin sensitisation, none of it informs on mutagenicity or repeated-dose, developmental and reproductive toxicity of the category members. Accordingly, this information is not considered as relevant to support prediction of all the endpoints under consideration.

In the absence of relevant supporting information, you have not established that the Substance and source substance [1] are likely to have similar properties. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

The lead registrants, on behalf of the respective joint submissions, have provided joint comments to the draft decisions sent by ECHA for the following substances, members of the N2-subgroup: C11'-MEA (EC 247-873-6); C12-MEA (EC 939-648-2); and C18-DEA (EC 308-072-8), i.e. the Substance, as well as for substance EC: 947-655-7.

In your comments to the draft decision you agree that there is limited supporting information specifically for the mutagenicity or repeated-dose, developmental and reproductive toxicity for the members of the N-2 subgroup, including your Substance. In order to address the data gaps, idenfified by ECHA as well as to support the read-across approach, you propose a tier-based strategy. In the first tier you propose to perform the OECD TG 422 study for all above-mentioned substances for the purposes of submitting bridging information for systemic and reproductive toxicity. You also propose to conduct genotoxicity studies with "*borderline*" substances or substances with "*worst-case molecular properties*." You claim that "*Based on this information and comparison, the decision will be taken to further test or apply read-across*"

[2] ECHA Guidance R.6: Section R.6.2.2.1.f

As this strategy relies essentially on data which is yet to be generated, no conclusion on the compliance of the potential read-across adaptation(s) can currently be made. As a consequence, there is currently no sufficient information that could be used to support your read-across. Should you decide to pursue the strategy presented in your comments, ECHA will assess its compliance in the follow-up to the present decision making process under Article 42(1) of the REACH Regulation. You remain responsible for complying with this decision by the set deadline.

(i) Adequacy and reliability of source studies

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

- 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 test method referred to in Article 13(3);
- cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter.

None of the following studies were performed according to the testing specifications set out in the corresponding OECD TGs:

- study (ii) , used to cover the requirement for sub-chronic toxicity
- study (iii), used to cover the requirement for pre-natal developmental toxicity

Therefore, the studies listed above are not adequate for the purpose of classification and labelling and/or risk assessment. The specific reasons are explained further below under the relevant information requirement sections (Appendix C, Sections 1 and 2).

II. Prediction outside of the subgroup N2

In your dossier you also refer for the following (eco)toxicological information requirements to studies conducted with the analogue substances that do not belong to the N2 subgroup:

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

- Butanedioic acid, sulfo-, 1,4-bis (2-ethylhexyl) ester, sodium salt; sodium 1,4-bis[(2-ethylhexyl)oxy]-1,4-dioxobutane-2-sulfonate (EC No. 209-406-4; CAS 577-11-7), member of the di-ester subgroup, hereafter referred as 'source substances [3]';

Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.)

- Aspartic acid, N-(3-carboxy-1-oxo-sulfopropyl)-N-(C16-C18 (even numbered), C18 unsaturated alkyl) tetrasodium salts (EC No. 939-704-6),member of the N3 subgroup, hereafter referred as 'source substance [4]';

Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

- source substances [3]

- Calcium bis{1,4-bis[(2-ethylhexyl)oxy]-1,4-dioxobutane-2-sulfonate} (EC No. 204-889-8); not included in any of the subgroups, hereafter referred as 'source substance [5].

Ready Biodegradability study (Annex VII, Section 9.2.1.1)

- Disodium C18-C22 sulphosuccinate; not included in any of the subgroups, hereafter referred as 'source substance [6].

You have provided the following reasoning for the prediction of the relevant toxicological properties of the Substance from these source substances:

With the the source substance [4]:
- "*Based on the safe and similar toxicity profile within the N2 (and N3) subgroup, further read across within these subgroups*" is possible to predict the human health properties of the members of the N2 subgroup including the Substance.

With the source substance [3]:
- "*based on the structural, kinetic/metabolic and toxicological similarity between subgroups, read across was also performed with the di-ester subgroup substance CAS 577-11-7"* to predict the reproductive and developmental toxicity properties of the members of the N2 subgroup including the Substance.

ECHA understands that you intend to use the properties of the aforementioned source substances to predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects.

ECHA has analysed the provided information and has identified the following issues.

A. Predictions of toxicological properties from N3 subgroup members

(i) Read-across hypothesis

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. 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 source substance(s) and your Substance[3]. 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.

Your read-across hypothesis is that the toxicological similarity between the members of N2 and N3 subgroups, in one or multiple endpoints is a sufficient basis for predicting the properties of the Substance for other endpoints.

Toxicological similarity in one or multiple endpoints does not necessarily lead to predictable or similar human health properties in other endpoints. You have not provided a well-founded hypothesis to establish a reliable prediction for systemic (target organ) toxicity, based on recognition of the structural similarities and differences between the different subgroups members.

(ii) *Missing 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*

[3] ECHA Guidance R.6.

data for reference substance(s)". For this purpose "*it is important to provide supporting information to strengthen the rationale for the read-across*"[4]. 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.

As indicated above, your read-across hypothesis is based on the assumption that the toxicological similarity between the members of N2 and N3 subgroups is a sufficient basis for predicting the systemic target-organ toxicity properties of the Substance (member of the N2 subgroup) for using data from the source substance [4] (member of the N3 subgroup). In this context, relevant, reliable and adequate information allowing to compare the properties of the N2 and N3 subroups 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 have not provided studies of comparable design and duration that allow comparison of the properties under consideration between the Substance and the source substance [4].

In the absence of such information, you have not established that the N2 and N3 subgroup members are likely to have similar systemic (target organ) toxicity. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

B. Predictions of toxicological properties from di-ester subgroup members

(i) Missing 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.

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 substances 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.

In your justification document you have claimed that there is a kinetic/ metabolic similarity between substances in the diester subgroup, i.e. the source substance [3] and the substances in the N2 subgroup. On this basis you predict the reproductive and developmental toxicity properties of your Substance from data, generated with source substance [3], member of the di-ester subgroup.

ECHA notes that your claim is not substantiated by data. Toxicokinetic data are available only for source substance [3]. The impact of the structural differences between source substance [3] and the members of the N2 subgroup including the Substance on their metabolism was not discussed. Therefore, it is not possible to conclude whether there is kinetic/ metabolic similarity between these substances in the absence of comparable data.

[4] ECHA R.6: Section R.6.2.2.1.f
[5] ECHA Guidance R.6, Section R.6.2.2.1.f

Hence, it is not possible to conclude that the toxicological properties for reproductive toxicity of the Substance could be predicted from the data obtained with the source substance [3] on the basis of kinetic/ metabolic similarity.

In the absence of such information, you have not established that the Substance and of the source substance [3] are likely to have similar properties. Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

(ii) Adequacy and reliability of source studies

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

- 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 test method referred to in Article 13(3);
- cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter.

None of the following studies were performed according to the testing specifications set out in the corresponding OECD TGs:

- studies (ii) and (iii) used to cover the requirement for reproductive toxicity

Therefore, the studies listed above are not adequate for the purpose of classification and labelling and/or risk assessment. The specific reasons are explained further below under the relevant information requirement sections Appendix B, Section 4.

C. Prediction of (eco)toxicological properties from source substance [5] and source substance [6]

(i) Absence of documentation

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 a justification for the read-across including a hypothesis, explanation of the rationale for the prediction of properties and robust study summary(ies) of the source study(ies).[6]

You have provided studies conducted with source substance [5] and source substance [6].

You have not provided documentation as to why this information is relevant for your Substance. In the absence of such documentation, ECHA cannot verify that the developmental toxicity properties of your Substance can be predicted from the data on the source substance [5] and on source substance [6].

In the absence of such documentation, ECHA cannot verify that the properties of your Substance can be predicted from the data on the source substances [5] and [6].

(ii) Adequacy and reliability of source study with source substance [6]

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

- be adequate for the purpose of classification and labelling and/or risk assessment;

[6] ECHA Guidance, Chapter R.6: Section R.6.2.6.2

To fulfil an information requirement or to be appropriate for an adaptation, the test material must be representative for the substance (Article 10 and Recital 19 of REACH; ECHA Guidance R.4.1). Therefore, the unambiguous characterisation of the composition of the test material used to generate the source data is required to assess whether the test material is representative for the source substance and thus relevant to the Substance.

The information provided in your dossier on the composition of the test material for the source study with source substance [6] is limited to the generic name of the substance ("[redacted]") and it does not contain the chemical identity and quantitative occurrence of its constituents. This issue concerns the following study (study listed under the relevant information requirement in Appendix A, Section 2):

- study (i) used to cover the requirement for ready biodegradability

Due to the above deficiency, an independent assessment of the representativity of the test material to the source substance [6] and of the relevance of the test material to the Substance cannot be conducted. Consequently, the study listed above is not adequate for the purpose of classification and labelling and/or risk assessment.

Conclusions on the grouping of substances and read-across approach

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

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

1. In vitro gene mutation study in bacteria

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

You have provided the following study record with source substance [2]:

i. *In vitro* gene mutation in bacterial cells (according to OECD TG 471) giving negative results

ECHA has assessed this information and identified the following issue(s):

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. As explained in the Appendix on Reasons common to several requests, your adaptation in accordance with Annex XI, Section 1.5. is rejected.

Therefore, the information requirement is not fulfilled.

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

Study design

To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471) is considered suitable.

2. Ready biodegradability

Ready biodegradability is an information requirement in Annex VII to REACH (Section 9.2.1.1.).

You have provided:

i. OECD 301B study with source substance [6]

ii. QSAR prediction for the Substance on ready biodegradability using *BIOWIN™ v4.10 module of EPI Suite™ v.4.00.*

ECHA has assessed this information and identified the following issue(s):

A. You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5 by providing study i. above with an analogue substance. As explained in the Appendix on Reasons common to several requests, your adaptation in accordance with Annex XI, Section 1.5. is rejected.

B. You have adapted this information requirement by using a Qualitative and quantitative structure activity relationship ((Q)SAR) under Annex XI, Section 1.3 by providing study ii. listed above.

According to Annex XI, Section 1.3., four conditions shall be necessarily fulfilled to use QSAR results instead of testing. Firstly, the prediction needs to be derived from a scientifically valid model. Secondly, the prediction must fall within the applicability domain of the model. Thirdly, results need to be adequate for the purpose of risk assessment or classification and labelling. Finally, adequate and reliable documentation about the applied method must be provided.

The documentation is considered adequate when it includes the information specified in or equivalent to the QSAR Model Reporting Format (QMRF) and QSAR prediction reporting format (QPRF) templates. The QMRF contains information on the source, type, development, validation, and possible applications of the model. In the QPRF, the prediction outcome is presented with some reasoning. The reliability of the prediction should also be assessed and provided.[7]

You have provided a generic description of the models in the QSAR endpoint study record in the dossier, and reported the generic outcome of the prediction. However, no QMRF and QPRF specific information was provided about the predictions.

In absence of specific information about the models and the prediction (i.e. QMRF and QPRF), ECHA cannot assess whether the substance falls within the applicability domain of the model and if the prediction is adequate for the purpose of risk assessment and/or classification and labelling.

Therefore, your adaptation in accordance with Annex XI, Section 1.3. is rejected.

On this basis, the information requirement is not fulfilled.

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

[7] ECHA Guidance R.6

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

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

An *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study is a standard information requirement in Annex VIII to REACH.

You have provided the following study record with source substance [2]:

i. *In vitro* micronucleus assay (according to OECD TG 487) giving negative results.

ECHA has assessed this information and identified the following issue(s):

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. As explained in the Appendix on Reasons common to several requests, your adaptation in accordance with Annex XI, Section 1.5. is rejected.

Therefore, the information requirement is not fulfilled.

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

Study design

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

2. In vitro gene mutation study in mammalian cells

An *in vitro* gene mutation study in mammalian cells is a standard information requirement in Annex VIII to REACH in case of a negative result in the *in vitro* gene mutation test in bacteria and the *in vitro* cytogenicity test.

Triggering

Your dossier contains inadequate data for *in vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.) and for *in vitro* cytogenicity study in mammalian cells (Annex VIII, Section 8.4.2.), performed with the source substance [2] which are rejected for the reasons provided in Appendix A, section 1. and Appendix B, Section 1.

The results of the requests for information in Appendix A, Section 1. and Appendix B, Section 1 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.

You have provided the following study record with source substance [2]:

(i) *In vitro* gene mutation in mammalian cells (according to OECD TG 476) giving negative results.

ECHA has assessed this information and identified the following issue(s):

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. As explained in the Appendix on Reasons common to several requests, your adaptation in accordance with Annex XI, Section 1.5. is rejected.

Therefore, the information requirement is not fulfilled.

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

Study design

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

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

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

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

You have provided the following study record with source substance [4]:

i. Sub-chronic (90-day) study in rats via diet (similar to OECD TG 408, pre-GLP, 1976)

ECHA has assessed this information and identified the following issue(s):

You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. As explained in the Appendix on Reasons common to several requests, your adaptation in accordance with Annex XI, Section 1.5. is rejected.

Therefore, the information requirement is not fulfilled.

The present decision requests the registrants concerned to generate and submit a reliable sub-chronic toxicity study (90 days) (see Appendix C, Section 1). According to Column 2 of Annex VIII, Section 8.6.1., and to prevent unnecessary animal testing, a short term toxicity study (28 days) does not therefore need to be conducted.

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

In the comments on the draft decision, you agree to perform the Short-term repeated dose toxicity (28 days; Annex VIII, Section 8.6.1.), combined with the Screening for reproductive/developmental toxicity study (OECD TG 422). ECHA acknowledges that you intend to use the study as bridging information to consolidate the predictions for the systemic toxicity properties of the Substance.

4. 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:

(i) Screening for reproductive/developmental toxicity study in rats (according to OECD TG 422) performed with source substance [1];
(ii) "Three-generation reproductive toxicity study" in rats (no OECD TG, non-GLP, 1986), performed with source substance [3];
(iii) "Two-generation reproductive toxicity study" in rats (no OECD TG, pre-GLP, 1970), performed with source substance [3].

ECHA has assessed this information and identified the following issue(s):

A. You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. As explained in the Appendix on Reasons common to several requests, your adaptation in accordance with Annex XI, Section 1.5. is rejected. Moreover, ECHA has identified an endpoint specific issue with regards to your adaptation that is addressed under point B below.

B. According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across should be adequate for the purpose of classification and labelling and/or risk assessment; and have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3).

The key parameters required by EU B.63/OECD TG 421 include, among others:

- Histopathology and weight of major non-reproductive organsExamination of parameters for sexual function and fertility such as weight and histopathology of reproductive organs and tissues;
- Monitoring of oestrus cyclicIty;
- Examination of offspring parameters such as anogenital distance, number of nipples, areolae in male pups.

Studies ii. and iii. conducted with source substance [3] have not investigated the above mentioned key parameters. Therefore, these studies do not have adequate and reliable coverage of the key parameters foreseen to be investigated in the OECD TG 421 and are not adequate for the purpose of classification and labelling and/or risk assessment.

On this basis, the information requirement is not fulfilled.

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

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[8] administration of the Substance.

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

Appendix C: 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 in Annex IX to REACH.

You have provided:

i. Sub-chronic (90-day) study in rats via diet (OECD TG 408, pre-GLP, 1976) performed with source substance [4];
ii. Screening for reproductive/developmental toxicity study in rats (key study; according to OECD TG 422) performed with source substance [1].

ECHA has assessed this information and identified the following issue(s):

A. You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. As explained in the Appendix on Reasons common to several requests, your adaptation in accordance with Annex XI, Section 1.5. is rejected. Moreover, ECHA has identified an endpoint specific issue with regards to your adaptation that is addressed under point B below.

B. According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across should 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 test method referred to in Article 13(3); and cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter.

The key parameters required by OECD TG 408 include, among others:

- administration of the Substance daily for a period of at least 90 days until the scheduled termination of the study.
- Hystopathological investigations of all organs, performed on at least 10 animals per sex/group

The study (ii) conducted with source substance [1] does not have the required exposure duration of 90 days as required in OECD TG 408. The exposure duration reported is approximately 63 days (for females) and 36 days (for males). Furthermore the organ weight and histopathological investigations in OECD TG 422 are only conducted using 5 animals per sex per group and not 10 per sex per group as in OECD TG 408. Therefore, this study does not have adequate and reliable coverage of the key parameters foreseen to be investigated in the OECD TG 408 and is not adequate for the purpose of classification and labelling and/or risk assessment.

In your comments to the draft decision you refer to the tier-based testing strategy relying on the generation of additional supporting information. For this information requirement you propose first to perform the Screening for reproductive/developmental toxicity study (OECD TG 422) with category members, including your Substance, which you intend to use as bridging information for predictions of the systemic and reproductive toxicity properties of the Substance. Based on the results obtained from these studies, you will decide whether to adapt this information requirement by read-across (Annex XI, Section 1.5) or whether to conduct the requested study with the Substance in a second phase.

As indicated in the Appendix on Reasons common to several requests no conclusion on the compliance of the intended tier-based testing strategy can currently be made. Should you decide to pursue the strategy presented in your comments, ECHA will assess its compliance

in the follow-up to the present decision making process under Article 42(1) of the REACH Regulation. You remain responsible for complying with this decision by the set deadline.

On this basis, the information requirement is not fulfilled

Study design

Following the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity[9]. 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:

i. Pre-natal developmental toxicity in rats via diet (equivalent to OECD TG 414, no GLP, 1976) performed with source substance [3];
ii. Pre-natal developmental toxicity in rats via diet (equivalent to OECD TG 414, no GLP, 1976), performed with source substances [5];
iii. Screening for reproductive/developmental toxicity study in rats (key study; according to OECD TG 422, GLP), performed with source substance [1].

ECHA has assessed this information and identified the following issue(s):

A. You have adapted this information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. As explained in the Appendix on Reasons common to several requests, your adaptation in accordance with Annex XI, Section 1.5. is rejected. Moreover, ECHA has identified an endpoint specific issue with regards to your adaptation that is addressed under point B below.

B. According to Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across should:be adequate for the purpose of classification and labelling and/or risk assessment; and have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3).

The key parameters required by OECD TG 414 include, among others:

- examination of the foetuses for sex and body weight; external, skeletal and soft tissue alterations (variations and malformations); number of resorptions and or live foetuses; measurement of anogenital distance in live rodent foetuses

The study (iii) conducted with source substance [1] has not investigated the above mentioned key parameters. Therefore, this study does not have adequate and reliable coverage of the key parameters foreseen to be investigated in the OECD TG 414 and is not adequate for the purpose of classification and labelling and/or risk assessment. Based on the above, the information requirement is not fulfilled.

In your comments to the draft decision you refer to the tier-based testing strategy relying on the generation of additional supporting information. For this information requirement you propose first to perform the Screening for reproductive/developmental toxicity study (OECD

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

TG 422) with category members, including your Substance, which you intend to use as bridging information for predictions of the systemic and reproductive toxicity properties of the Substance. Based on the results obtained from these studies, you will decide whether you will adapt this information requirement by read-across (Annex XI, Section 1.5) or whether you will conduct the requested study with the Substance in a second phase.

As indicated in the Appendix on Reasons common to several requests no conclusion on the compliance of the intended tier-based testing strategy can currently be made. Should you decide to pursue the strategy presented in your comments, ECHA will assess its compliance in the follow-up to the present decision making process under Article 42(1) of the REACH Regulation. You remain responsible for complying with this decision by the set deadline.

Study design

A PNDT study according to the test method OECD TG 414 should be performed in rat or rabbit as preferred species with oral[10] administration of the Substance.

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

Appendix D: 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[11].

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:
   - the variation in compositions reported by all members of the joint submission,
   - the boundary composition(s) of the Substance,
   - the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

2. Information on the Test Material needed in the updated dossier
   - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance. Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[12].

[11] https://echa.europa.eu/practical-guides
[12] https://echa.europa.eu/manuals

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 08 April 2020.

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

ECHA took into account your comments. ECHA is currently reviewing its overall approach as to the examination of exposure based adaptations under Section 3.2 (a) of Annex XI and no definite conclusions have been reached yet. For that reason, the long-term aquatic toxicity requests (C.3 and C.4) have been removed from the draft decision. However, please note that this does not prevent ECHA from opening a compliance check at a later stage to address these endpoints.

Deadline to submit the requested information in this decision

In the draft decision communicated to you, the time indicated to provide the requested information was 24 months from the date of the adoption of the decision. In your comments on the draft decision you requested ECHA to extend the deadline to a total of 36 months to ensure adequate time to cover the testing programme phases 1 and 2, including the preparation of the test materials, decision process between phase 1 and 2 and the IUCLID dossier generation. You provided a statement from a CRO, indicating that based on the current capacity of the laboratory, 36 months is more relevant timeline.

ECHA took into account the reasoning of your request for an extension of the deadline. ECHA considers that a deadline of 36 months from the adoption of the decision is sufficient to enable performing and submitting the study under the current circumstances.

Therefore, ECHA has granted the requested extension and set the deadline to 36 months.

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[13] 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)[14]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[14]

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[15]
Guidance Document on aqueous–phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

[13] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[14] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[15] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

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.