~~Confidential~~

Helsinki, 06 May 2022

Addressees
Registrant(s) of alcohol C9, br and lin as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
10/12/2012

Registered substance subject to this decision ("the Substance")
Substance name: nonanol, branched and linear
EC number: 614-557-8

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 ***13 November 2023***.

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

A. Information required from all 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. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: EU C.2./OECD TG 202)

3. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: EU C.3./OECD TG 201)

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

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

2. If negative results are obtained in test performed for the information requirements 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. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: EU B.63/OECD TG 421) by oral route, in rats

4. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: OECD TG 203)

C. 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 aquatic invertebrates (Annex IX, Section 9.1.5.; test method: EU C.20./OECD TG 211)

4. 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 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, 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 Mike Rasenberg, 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 the weight of evidence adaptations**

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

- 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.)
- 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.)

You reasoning for the weight of evidence adaptation is: the Substance is a member of the category 'C6-24 Alcohols. Long Chain Alcohols (C6-24 primary aliphatic alcohols; linear and essentially linear)' Whenever, sufficient data on the Substance is missing the data gap is filled using weight of evidence based on read-across from other category members.

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.

In any weight of evidence justification, the integration of the sources of information is fundamental to support a robust conclusion on whether the Substance has a particular dangerous property. Three main aspects must be addressed: 1) Analysis of the extent to which the composition of the Substance is covered by the sources of information; (2) Analysis of the extent to which the hazard data obtained from the sources of information reliably cover the key aspects that is foreseen to be investigated by study normally required for the information requirement(s) where weight of evidence is invoked; and (3) Analysis of the residual uncertainty.

The Substance is a UVCB (unknown or variable composition, complex reaction products or of biological materials) substance composed of linear and branched C9 alcohols.

The sources of information provided have mainly been conducted using mono- or multi constituent substances or UVCB substances. You have not explained to what extent each source of infromation cover the composition of the Subtance.

Furthermore, you have not explained how the hazard data obtained with the sources of information, considering the relevance, reliability, coverage, consistency and results, can be brough together to reach conclusion on whether or not the Substance has a particular dangerous property with regard each of the infromation requirement(s).

Moreover, you have not analysed the residual uncertainty associated with the weight of evidence conclusion for each infromation requirment.

Based on the above, ECHA concludes that you have not provided adequate documentation to support robust conclusions for your weight of evidence adaptations.

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 below, while the specific ones are set out under the information requirement concerned in the Appendices A to C.

1.1. Reliability of the provided information with analogue substances

ECHA understands that you use data obtained with analogue substances in a read-across approach as part of your weight of evidence adaptation. For this information to reliably contribute to the weight of evidence approaches, it would have to meet the requirements for Grouping of substances and read-across approaches.

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).

Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance[2] and related documents[3, 4].

Description of the grouping

In the CSR, you refer to a category of 'C6-24 Alcohols. Long Chain Alcohols (C6-24 primary aliphatic alcohols; linear and essentially linear)'. You identify the members of the category members and provide a category justification document in the CSR.

You define the the structural basis for the grouping as: a family of primary aliphatic alcohols within a carbon chain length range of C6-C24, limited to linear and essentially-linear alcohols. ECHA understands that this is the applicability domain of the grouping and has assessed your predictions on this basis.

1.2. Predictions for toxicological properties

[2] ECHA Guidance R.6
[3] Read-Across Assessment Framework (RAAF)
[4] Read-across assessment framework (RAAF) - considerations on multi-constituent substances and UVCBs

You provide a read-across justification in the CSR.

For toxicological properties you read-across to the Substance from the following source substances:

- dodecan-1-ol, EC No. 203-982-0;
- octan-1-ol, EC No. 203-917-6;
- tetradecan-1-ol (Alcohols, C10-16), EC No. 267-019-6;
- Alcohols, C6-12, EC No. 271-642-9
- 2-ethylhexan-1-ol, EC No. 203-234-3.

You provide the following reasoning for the predictions of toxicological properties: "The hypothesis is that the long chain linear aliphatic alcohol Category has, at its centre, an homologous series of increasing carbon chain length alcohols. The structure of the Category is associated with a consistency and predictability in the physicochemical, environmental, and toxicological property data across its members. In addition, certain branched and unsaturated structures are considered to have such similar properties that their inclusion in the category is well justified."

"For all forms of repeated dose, reproductive and developmental effects and sensitisation, there is sufficient evidence for no effects at the maximum deliverable dose and this conclusion does not vary with carbon number."

"For all forms of genetic toxicity, there is sufficient evidence for no effects and this conclusion does not vary with carbon number."

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 to be quantitatively equal to those of the source substance.

ECHA notes the following shortcomings with regards to predictions of toxicological properties. They are common to all the information requirements for which you refer to read-across information, unless their limited application is indicated in the title:

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" (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.). 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 the source substance(s).

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 substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substance(s) 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 Substance and of the source substance(s).

The Substance contains branched AND linear alcohols. You have not provided supporting information addressing the impact on the toxicological properties of allowed variations in structural elements; i.e. linear alcohols, branched alcohols, and position of the branching within the alcohols. While there is information on the UVCB substances which may contain various linear and branched components, there are no information on test substance composition to confirm the coverage of the constituents tested (see below) or the test substance(s) are not covering the structural elements present in the target substance. You have not provided any supporting information to mitigate this fact.

ECHA also notest that you have provided additional summaries of information and data matricies in the CSR. As the information on these studies provided in the CSR is limited and not sufficient for an independent evaluation, this informaiton has not been further considered in this assessment of your adaptation.

For the reasons presented above, it is not possible to demonstrate that the toxicity profile of the Substance containing linear and branched components can be predicted from the source substances. There are no supporting information to explain why the structural differences do not influence toxicokinetics and toxicodynamics of the substances.

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

Missing information on the test material

Under Annex XI, Section 1.5., if the grouping concept is applied then in all cases the results to be read across must be adequate for the purpose of classification and labelling and/or risk assessment.

In order to predict the properties of the Substance, the test material used in the study on the source substance must be representative for the source substance (Article 10 and Recital 19 of REACH; Guidance on IRs and CSA, Section R.4.1.). Therefore, an 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.

For most of the studies provided, you have identified the test material by name and chemical identifiers, without further information, including composition of the test material.

In the absence of the information on the composition, impurities of the test material, you have not demonstrated that the test material is representative for the source substance. Therefore, the study is not adequate for the purpose of classification and labelling and/or risk assessment.

1.3. Conclusion on the reliability of the information on the analogue substances

Based on the above, the information from the analogue substances cannot reliably contribute to your weight of evidence adaptations.

1.4.Information provided in your comments on the draft decision

In your comments to the draft decision, you do not agree to perform the requested studies for the following endpoints:

- 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.)
- Pre-natal developmental toxicity study in a second species (Annex X, Section 8.7.2.)

Instead, you now indicate your intention to adapt all the above standard information requirements by means of grouping and read-across according to Annex XI, Section 1.5, of the REACH Regulation.

You "acknowledge the need to strengthen the mentioned endpoints to ensure that the chemical safety assessment is robust" and accept the rejection of the adaptations of the information requirements. Rather than conducting the tests required in the decision, you propose "to perform sufficient studies to support the toxicity information requirements of the C6-C24 alcohols within the category using a targeted testing approach, applying the scientific rationale for the use of those data in a read-across strategy".

You present a tiered testing strategy for the generation of additional supporting information on some category members.

More specifically, you intend to conduct approximately five combined repeated dose toxicity studies with the reproduction/developmental toxicity screening tests (OECD TG 422) with linear, branched and linear and unsaturated substances; an oral Sub-chronic toxicity study (OECD TG 408) will be conducted on Alcohols, C9-11, branched and linear (EC No. 288-284-4); and Pre-natal developmental toxicity studies (OECD TG 414) in the first and second specied will be conducted on Alcohols, C9-11, branched and linear (EC No. 288-284-4); C6 linear (CAS 111-27-3; EC 203-852-3); and C24 linear (CAS 506-51-4; EC 208-043-9).

Thereafter, the decision to read across data between category members or conduct more tests on additional category members will then be made accordingly.

Based on your comments ECHA understands that you accept the reasoning for the rejection of the adaptations currently in the registration.

ECHA acknowledges your intention to generate additional data and to strengthen the support for a read-across approach within the category of C6-C24 Alcohols. However, ECHA notes the following.

Firstly, as indicated in your comments, the testing strategy relies on data which is yet to be generated and an anticipated outcome of these tests. Therefore, your testing strategy does not allow for a clear conclusion on compliance with the information requirements for the substances concerned.

Secondly, the current compliance checks concern three substances, i.e. Alcohols, C9-11, branched and linear (EC No. 288-284-4), Nonanol, branched and linear (EC No. 614-557-8; i.e. the Substance), and Alcohols, C12-C13, branched (EC No. 941-187-7).

In contrast, your testing strategy aims to achieve compliance for a larger group of substances, i.e the entire category of C6-C24 Alcohols, which is well beyond the scope of the this compliance check.

Thirdly, you propose to conduct five combined repeated dose toxicity studies with the reproduction/developmental toxicity screening tests (OECD TG 422) to strengthen the support for your read-across approach across the category. However, the identity of the category members to be tested in these OECD 422 studies are uncertain at this point in time.

It is not possible to assess, based on the informaton curently available, whether these proposed studies would support read-across for the Substance. This is because the substances tested may differ in their structures from the constituents of the Substance, in particular on the length of the carbon chain. Therefore the results from the supporting studies may not

directly inform on the properties of some of constituents of the Susbtance and further explanations may be needed in order to reliably use this information to predict the properties of the Substance

Regardless, you may at your own discretion generate any additional information to support read-across within the categogry of C6-C24 Alcohols; as long as the tests conducted are not listed in Annexes IX or X to REACH.

In summary, as your strategy relies on a read-across hypothesis and on supporting information that needs to be fully described and justified, as well as on data/information which is yet to be generated for the proposed category members, no conclusion on the compliance of the proposed adaptation can be made. You remain responsible for complying with this decision by the set deadline.

2. Assessment of the read-across adaptations for ecotoxicological properties.

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

- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

ECHA has considered the scientific and regulatory validity of your read-across approach(es) in general before assessing the specific standard information requirements in the following 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 '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[5,6].

A. Predictions for ecotoxicological properties

You have provided a read-across justification in IUCLID Section 6.1.

You predict the properties of the Substance from the structurally similar substance nonan-1-ol (EC No. 205-583-7), i.e. the source substance.

You have provided the following reasoning for the prediction of aquatic toxicity: "*The nonanol, branched and linear substance has a structure which is termed 'essentially linear'. The physicochemical, toxicological and ecotoxicological properties and behaviour of this substance do not significantly differ between such structures and their linear analogues. It is therefore possible to read-across between the two substances. Additionally these isomeric substances*

[5] 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)

[6] 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

have an identical molecular weight. The difference in composition is dependent on the manufacturing process which may create linear alcohols or simple mono-branched structures. Direct read-across from nonanol (CAS 143-08-8) to nonanol, branched and linear (CAS 68515-81-1) is scientifically justified and valid."

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 to be quantitatively equal to those of the source substance.

ECHA notes the following shortcoming(s) with regards to prediction(s) of aquatic toxicity.

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*" (Guidance on IRs and CSA R.6, Section R.6.2.2.1.f.). 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 the source substance(s).

Supporting information must include e.g. supporting information and bridging studies to compare properties of the Substance and source substances.

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

The Substance and the source substance have the same carbon chain length (i.e. C9), but the source substance is linear and the Substance contains both linear C9 (typical concentration >0 - ≤75%) and branched C9 alcohol constituents. To support your claim that the source substance and the Substance have similar ecotoxicological properties irrespective of branching, you refer to identical molecular weights.

Your registration dossier provides short-term toxicity to fish and to aquatic invertebrates studies with the source substance, and no aquatic toxicity studies with the Substance.

From the information provided, it is not possible to compare the properties of the Substance and of the source substance. In particular, the short-term toxicity to aquatic invertebrates with the source substance cannot be considered a reliable study, for the reasons explained further below under the relevant information requirement section A.2 Furthermore, the aquatic toxicity studies with the source substance only cover the C9 linear aspect of the composition of the Substance. However, the rest of the composition of the Substance is not covered and you have provided no supporting information which demonstrates that the ecotoxicity profiles of C9 branched is similar to that of C9 linear.

Thus the data set reported in the technical dossier does not include relevant, reliable and adequate information for the Substance and for the source substance(s) to support your read-across hypothesis.

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

B. 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 analogue substance. In addition, there are shortcoming(s) specific to one endpoint that are discussed under the relevant information requirement section A.2, which add to the failure to meet the requirements of Annex XI, Section 1.5. 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.

Information provided in your comments on the draft decision regarding the environmental endpoints

In your comments to the initial draft decision, you do not agree to perform the requested studies for the following environmental endpoints:

- Short-term toxicity in aquatic invertebrates (Annex VII, Section 9.1.1.)
- Growth inhibition study on algae (Annex VII, Section 9.1.2.)
- Short-term toxicity in fish (Annex VIII, Section 9.1.3.)
- Long-term toxicity in aquatic invertebrates (Annex IX, Section 9.1.5.)
- Long-term toxicity in fish (Annex IX, Section 9.1.6.)

Instead, you now indicate your intention to adapt all the above standard information requirements by means of grouping and read-across according to Annex XI, Section 1.5, of the REACH Regulation.

In your proposed read-across adaptation, you refer to a C6-24 Alcohols Category, which consists of a family of primary aliphatic alcohols with carbon chain lengths in the range C6-C24. The category members have varied compositions and are linear or have a single short-chain alkyl side-branch at the 2-position in the alkyl chain (usually an α-methyl or α-ethyl group).

In the comments, you propose a strategy relying on the generation of further evidence to strengthen the category approach and for this you indicate your intention to first undertake a new programme of literature research and QSAR modelling. You indicate that you then intend to incorporate in the category data any new experimental data available for substances within the chain length of the category members and you will then reassess the selection of key studies.

You also indicate that you intend to do this "*together with experimental work as necessary*" and you further specify that "*Short-term toxicity data may be generated (preferably for single constituent mono-branched alcohols) as needed, to ensure that sufficient relevant evidence is available to justify the category approach for the ecotoxicity endpoints and for validation of QSARs*". You do not specify which category members you intend to use in experimental testing other than your proposal to conduct OECD TG 210 tests in C6 and C14 linear saturated alcohols (Hexan-1-ol (EC 203-852-3) and Tetradecanol (EC 204-000-3)) within the category. You expect that these substances are at the extremes of the range where ecotoxicity effects may be observed.

In the comments, you further acknowledge that the category approach and the use of data for purposes of exposure assessment and risk characterisation could be documented more clearly and you commit to improve the documentation in the dossier update.

In the comments, you also foresee that validated QSAR predictions based on logKow are likely to be applicable since the mechanism of action for the category member alcohols is narcosis and a consistent trend in ecotoxicity correlated with carbon number is expected.

ECHA acknowledges your intention to generate additional information/data and your plans to refine the read-across approach.

However, as your strategy relies on a read-across hypothesis and on supporting information that needs to be fully described and justified, as well as on data/information which is yet to be generated for the proposed category members (including bridging studies and supporting information), no conclusion on the compliance of the proposed adaptation can be made. You remain responsible for complying with this decision by the set deadline.

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 an information requirement under Annex VII to REACH (Section 8.4.1.).

2.1. Information provided for the information requirement

You have adapted this information requirement by using Weight of evidence based on the following experimental data with substances other than the Substance:

i. Bacterial reverse mutation assay (1982) conducted with octan-1-ol, EC No. 203-917-6.
ii. Bacterial reverse mutation assay (1996) conducted with octan-1-ol (Alcohols, C6-12), EC No. 271-642-9.
iii. In vitro mammalian chromosome aberration test (1998) conducted with tetradecan-1-ol (Alcohols, C10-16), EC No. 267-019-6.
iv. In vitro mammalian cell gene mutation test (1983) conducted with 2-ethylhexan-1-ol, EC No. 203-234-3.
v. Mammalian bone marrow chromosome aberration test (1983) conducted with 2-ethylhexan-1-ol, EC No. 203-234-3. 50 cells
vi. Mammalian erythrocyte micronucleus test (1992) conducted with dodecan-1-ol, EC No. 203-982-0.
vii. Rodent dominant lethal test (reported in WHO, 1993) conducted with 2-ethylhexan-1-ol, EC No. 203-234-3.

1.1. Assessment of the information provided

You have adapted this information requirement using weight of evidence under Annex XI, Section 1.2.

As explained under Appendix on Reasons common to several requests, 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 8.4.1 at Annex VII include:

- Detection and quantification of gene mutations (base pairs, substitution, or frame shift) in cultured bacteria including data on the number of revertant colonies; and
- Data provided on 5 bacterial strains: four strains of S. typhimurium (TA98; TA100; TA1535; TA1537 or TA97a or TA97) and one strain which is either S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101).

We have assessed the individual sources of information with regard to relevance and identified the following issue(s):

Sources of information (iii-vii) have not investigated gene mutation in bacteria. Consequently, these studies do not provide relevant information for this information requirement.

The source of information (i-ii) provide information on gene mutations in bacteria. However, both studies were performed with 4 strains. The fifth strain *S. typhimurium* TA102 or *E. coli* WP2 uvrA or *E. coli* WP2 uvrA (pKM101) is missing. Concequently, the sources of information provide partially relevant infromation on gene mutation in bacteria.

In addition, they have the following deficiencies affecting their reliability:

Reliability of read-across predictions

As explained in Section 1.1. of the Appendix common to several requests, you have not demonstrated that you reliably can predict the properties of the Substance by using test results obtained with analogue substances.

Conclusion on the weight of evidence

As indicated above, the sources of infromation provide only partially relevant information for the information requirement, as the 5th strain is missing. In addition, the reliability of this information is hampered by the use of read-across which increases the uncertainty of the conclusion for the Substance. In addition, as explained in the Annex common to several requests, you have not provided adequate documentation addressing how you integrate the evidence to reach a robust conclusion on the weight of evidence.

Therefore, it is not possible to conclude, based on any source of information alone or together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 471 test.

Based on the above, your adaptation is rejected and the information requirement is not fulfilled.

1.2. Information on study design

To fulfil the information requirement for the Substance, the *in vitro* gene mutation study in bacteria (OECD TG 471, 2020) is considered suitable.

In the comments to the draft decision, you agree to conduct the test.

2. Short-term toxicity testing on aquatic invertebrates

Short-term toxicity testing on aquatic invertebrates is a standard information requirement in Annex VII to REACH.

2.1 Information provided for the information requirement

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

i. a non-guideline study that you conclude to be in accordance with OECD TG 202, conducted with source substance Nonan-1-ol (EC No. 205-583-7, CAS No. 143-08-8)

2.2 Assessment of the information provided

We have assessed this information and identified the following issues:

As explained in the Appendix on general considerations, your adaptation based on grouping of substances and read-across approach under Annex XI, Section 1.5 is rejected. In addition, ECHA identified endpoint specific issue(s) addressed below.

Under Annex XI, Section 1.5., the results to be read across must have an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3), in this case the OECD TG 202, and meet the requirements of the OECD GD 23 if the substance is difficult to test. Therefore, the following specifications must be met:

a) the concentrations of the test material are measured at least at the highest and lowest test concentration, at the beginning and end of the test;
b) young daphnids, aged less than 24 hours at the start of the test, are used.

Your Substance is considered as difficult to test, due to the reasons described below in section 2.3

Your registration dossier provides an OECD TG 202 study (i) with the source substance showing the following:

a) no analytical monitoring of exposure was conducted;
b) the test was not conducted on young daphnids but on adult copepods *Nitocra spinipes*.

The fact that the test concentrations in the study (i) are not analytically monitored despite the expected instability of the hydrophobic, surface active and readily biodegradable Substance in water is considered a critical methodological deficiency resulting in the rejection of the study results. Further, the test was not conducted with *Daphnia* species and the adult test organisms were used. The sensitivity of adult test organisms might be lower and cause increased uncertainty in the derived effect value.

Therefore, the study submitted in your adaptation, as currently reported in your dossier, do not provide an adequate and reliable coverage of the key parameter(s) in the corresponding OECD TG.

Therefore, your read-across approach under Annex XI, Section 1.5. is rejected.

On this basis, the information requirement is not fulfilled.

Your comments on the draft decision are addressed in section 2 of the Appendix on Reasons common to several requests above.

2.3 Study design

The Substance is difficult to test due to the high hydrophobicity (logKow 4.49), surface activity (surface tension 17.8 mN/m) and the expected instability of the readily biodegradable Substance. The OECD TG 202 specifies that, for difficult to test substances, you must consider the approach described in the 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 the OECD TG 202. 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 solutions.

3. Growth inhibition study aquatic plants

Growth inhibition study aquatic plants is an information requirement under Annex VII to REACH (Section 9.1.2.).

3.1 Information provided for the information requirement

You have provided the following justification to omit the study "*An EC50 value in the range 1 -10 mg/L has been estimated for the effects of decanol, branched and linear on algal growth. The estimate is based on expert judgement, which takes into consideration measured and predicted ecotoxicity values for other trophic levels and the relative susceptibility of algae*

compared to such trophic levels, in the same substance category. The estimation has been determined as a range due to the uncertainty associated with this kind of prediction."

3.2 Assessment of the information provided

We have assessed this information and identified the following issues:

A registrant may only adapt this information requirement based on the specific rules for adaptation set out in Column 2 of Annex VII, Section 9.1.2. or the general rules for adaptation set out in Annex XI. Adapting the information requirement in accordance with the general rules for adaptation set out in Annex XI requires identifying clearly the specific legal basis of the adaptation invoked and complying with relevant conditions listed in the corresponding section of Annex XI. In all cases, adequate and reliable documentation must be provided, including relevant justification and study records.

You have adapted this information requirement by referring to expert judgement and read-across. You provide an Endpoint Study Summary in your IUCLID dossier where you include a table with E(L)C50 values for algae, fish and daphnids for "*single carbon chain length alcohols and commercial products (multi-constituent substances)*". You also further specify that "*rather than just reading-across a single value from a different substance, this has also involved taking measured and predicted data for different trophic levels into account so as to factor in any consistent patterns in their relative susceptibilities.*"

Your argumentation is based on expert judgement on the basis of differences in sensitivities among trophic levels, which does not refer to any legal grounds for adaptation under Annex XI to REACH nor to any specific rule set out in Column 2 for this endpoint. Although you refer at one point to 'read-across' you also make it clear, in another point, that you rather use predicted data for different trophic levels. Your argumentation further refers to read-across, which is an adaptation possibility under Section 1.5 of Annex XI. However, no documentation (e.g. study records with source substances) is provided for this endpoint in the IUCLID dossier.

On this basis, your adaptation is rejected and the information requirement is not fulfilled.

Your comments on the draft decision are addressed in section 2 of the Appendix on Reasons common to several requests above.

3.3 Study design

The OECD TG 201 specifies that for difficult to test substances the OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.2.

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 an information requirement under Annex VIII to REACH (Section 8.4.2.).

1.1. Information provided for the information requirement

You have adapted this information requirement by using Weight of evidence based on the following experimental data with substances other than the Substance:

i. Bacterial reverse mutation assay (1982) conducted with otan-1-ol, EC No. 203-917-6.
ii. Bacterial reverse mutation assay (1996) conducted with octan-1-ol (Alcohols, C6-12), EC No. 271-642-9.
iii. In vitro mammalian chromosome aberration test (1998) conducted with tetradecan-1-ol (Alcohols, C10-16), EC No. 267-019-6.
iv. In vitro mammalian cell gene mutation test (1983) conducted with 2-ethylhexan-1-ol, EC No. 203-234-3.
v. Mammalian bone marrow chromosome aberration test (1983) conducted with 2-ethylhexan-1-ol, EC No. 203-234-3. 50 cells
vi. Mammalian erythrocyte micronucleus test (1992) conducted with dodecan-1-ol, EC No. 203-982-0.
vii. Rodent dominant lethal test (reported in WHO, 1993) conducted with 2-ethylhexan-1-ol, EC No. 203-234-3.

1.2. Assessment of the information provided

You have adapted this information requirement using weight of evidence under Annex XI, Section 1.2.

As explained under Appendix on Reasons common to several requests, 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 8.4.2. at Annex VIII includes:

- Detection and quantification of structural or numerical chromosomal aberrations in cultured mammalian cells including data on the cytotoxicity and the frequency of cells with chromosomal aberrations or micronuclei.

We have assessed the individual sources of information with regard to relevance and identified the following issue(s):

The sources of information (i), (ii), (iv) and (vii) have not investigated chromosomal aberrations in mammalian cells. Consequently, these studies do not provide relevant information.

The sources of information (iii), (v) and (vi) provide relevant information on chromosomal aberrations in mammalian cells.

However, they have the following deficiencies affecting their reliability:

Reliability of read-across predictions

As explained in Section 1.1. of the Appendix common to several requests, you have not demonstrated that you reliably can predict the properties of the Substance by using test results obtained with analogue substances.

Results obtained from study (iii) not fully reliable when compared to the OECD TG 473

Investigations/specifications in an *in vitro* mammalian chromosome aberration test (OECD TG 473) include that at least 300 well-spread metaphases must be scored per concentration.

In the source of information (iii), the following investigations/specifications are not to the requirements of OECD TG 473 as the study scored 200 cells per concentration.

Based on the above, the reliability of the contribution of the results obtained from this study to the weight of evidence is limited. The lower statistical power of the study introduces uncertainty in the results which must be considered.

Results obtained from study (v) is not fully reliable when compared to the OECD TG 475

Investigations/specifications in a Mammalian bone marrow chromosome aberration test (OECD TG 475) include:

a) The highest dose studied must be the maximum tolerated dose (MTD), i.e. the highest dose that is tolerated without evidence of toxicity (e.g. body weight depression or hematopoietic system cytotoxicity, but not death or evidence of pain, suffering or distress necessitating humane euthanasia). The highest dose can also be a dose that produces toxicity in the bone marrow.
b) The mitotic index must be determined as a measure of cytotoxicity in at least 1000 cells per animal for all treated animals (including positive controls), untreated or vehicle/solvent negative control animals.
c) At least 200 metaphases must be analysed for each animal for structural chromosomal aberrations including and excluding gaps.

In the source of information (v), the following investigations/specifications are not to the requirements of OECD TG 475:

a) The highest dose in the study correspond to about one fifth of the LD_{50}; this is well below the MTD.
b) You provide a mitotic index, however you to have not explained how many cells were counted to calculate the index.
c) The study has counted 50 cells when 200 well spread metaphases should be analysed.

Based on the above, the reliability of the contribution of the results obtained from this study to the weight of evidence is limited. The lower statistical power of the study and the unclarity regarding how the results were obtained introduce uncertainty in the results which must be considered.

Results obtained from study (vi) is not fully reliable when compared to the OECD TG 474

Investigations/specifications in a Mammalian erytrocyte microneucleus test (OECD TG 474) include that the proportion of immature among total (immature + mature) erythrocytes must be determined for each animal (by counting a total of at least 2000 erythrocytes for peripheral blood).

In the source of information (vi), the following investigations/specifications are not to the requirements of OECD TG 474 as the study has counted 1000 erythrocytes.

Based on the above, the reliability of the contribution of the results obtained from this study to the weight of evidence is limited. The lower statistical power of the study introduces uncertainty in the results which must be considered.

Conclusion on the weight of evidence

As indicated above, the sources of infromation provide relevant information for the information requirement, but the reliability of this infromation is hampered by the use of read-across and issues related to how the results were obtained in the studies which increases the uncertainty of the conclusion for the Substance. In addition, as explained in the Annex common to several requests, you have not provided adequate documentation addressing how you integrate the evidence to reach a robust conclusion on the weight of evidence.

Therefore, it is not possible to conclude, based on any source of information alone or together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in a OECD TG 473 or OECD TG 487 test.

Based on the above, your adaptation is rejected and the information requirement is not fulfilled.

1.3. Information on study design

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

In the comments to the draft decision, you agree to conduct the study.

2. 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.

The result of the requests for information in the Sections 1 of Appendix A and of this Appendix 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.

2.2. Information provided for the information requirement

You have adapted this information requirement by using Weight of evidence based on the following experimental data with substances other than the Substance:

i. Bacterial reverse mutation assay (1982) conducted with otan-1-ol, EC No. 203-917-6.
ii. Bacterial reverse mutation assay (1996) conducted with octan-1-ol (Alcohols, C6-12), EC No. 271-642-9.
iii. In vitro mammalian chromosome aberration test (1998) conducted with tetradecan-1-ol (Alcohols, C10-16), EC No. 267-019-6.
iv. In vitro mammalian cell gene mutation test (1983) conducted with 2-ethylhexan-1-ol, EC No. 203-234-3.
v. Mammalian bone marrow chromosome aberration test (1983) conducted with 2-ethylhexan-1-ol, EC No. 203-234-3. 50 cells
vi. Mammalian erythrocyte micronucleus test (1992) conducted with dodecan-1-ol, EC No. 203-982-0.
vii. Rodent dominant lethal test (reported in WHO, 1993) conducted with 2-ethylhexan-1-ol, EC No. 203-234-3.

2.1. Assessment of the information provided

You have adapted this information requirement using weight of evidence under Annex XI, Section 1.2.

As explained under Appendix on Reasons common to several requests, 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 8.4.3 at Annex VIII includes similar information that is produced by the OECD TG 476/490 and OECD TG 488. This includes:

- Detection and quantification of gene mutations (point mutations, frame-shift mutations, small deletions, etc.) including data on the frequency of mutant colonies in cultured mammalian cells (in vitro) or mutant frequency for each tissue in mammals (in vivo).

We have assessed the individual sources of information with regard to relevance and identified the following issue(s):

The sources of information (i) to (iii) and (v) to (vii) have not investigated gene mutation in mammalian cells. Consequently, these studies do not provide relevant information.

The source of information (iv) provides relevant information on gene mutation in mammalian cells.

However, there are deficiencies affecting its reliability:

Reliability of read-across predictions

As explained in Section 1.1. of the Appendix common to several requests, you have not demonstrated that you reliably can predict the properties of the Substance by using test results obtained with analogue substances.

Results obtained from study (iv) is not fully reliable when compared to the OECD TG 476

Investigations/specifications in an In vitro mammalian cell gene mutation tests using the Hprt and xprt genes (OECD TG 476) include:

a) 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.
b) Data on the cytotoxicity and the mutation frequency for the treated and control cultures must be reported.

In the source of information (iv), the following investigations/specifications are not to the requirements of OECD TG 476:

a) You to not state which positive control was used nor do you provide data on the cytotoxicity and the mutation frequency for the positive control
b) You have not provided data on the cytotoxicity and the mutation frequency for the treated and control cultures.

Based on the above, the reliability of the contribution of the results obtained from this study to the weight of evidence is limited. The unclarity regarding how the results were obtained introduce uncertainty in the results which must be considered.

Conclusion on the weight of evidence

As indicated above, while one source of infromation provide relevant information for the information requirement, the reliability of this infromation is hampered by the use of read-across and issues related to how the results were obtained which increases the uncertainty of the conclusion for the Substance. In addition, as explained in the Annex common to several requests, you have not provided adequate documentation addressing how you integrate the evidence to reach a robust conclusion on the weight of evidence.

Therefore, it is not possible to conclude, based on any source of information alone or together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 476 or OECD TG 490 test.

Based on the above, your adaptation is rejected and the information requirement is not fulfilled.

2.2. Information on 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.

In the comments to the draft decision, you agree to conduct the study.

3. Screening for reproductive/developmental toxicity

Screening for reproductive/developmental toxicity is a standard information requirement under 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.

3.1. Information provided for the information requirement

You have adapted this information requirement by using Weight of evidence based on the following experimental data:

(i) combined Repeat dose and Reproductive/Developmental Toxicity Screening Test (1992) conducted with dodecan-1-ol, EC No. 203-982-0.
(ii) sub-chronic toxicity study (90 days; 1966) conducted with hexan-1-ol, CAS No. 111-27-3.

3.2. Assessment of the information provided:

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

You have adapted this information requirement using weight of evidence under Annex XI, Section 1.2.

As explained under Appendix on Reasons common to several requests, 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 8.7.3 at Annex VIII includes similar information that is produced by the EU B.63/OECD TG 421 or EU B.64/OECD TG 422. At general level, it includes information on the following key elements: 1) sexual function and fertility, 2) toxicity to offspring, and 3) systemic toxicity in parental generation.

We have assessed the individual sources of information with regard to relevance and identified the following issue(s):

Aspect 1) sexual function and fertility

Sexual function and fertility on both sexes must include information on mating, fertility, gestation (length), maintenance of pregnancy (abortions, total resorptions), parturition, lactation, organ weights and histopathology of reproductive organs and tissues, litter sizes, nursing performance and other potential aspects of sexual function and fertility.

The source of information (i) provides relevant information on aspect 1).

The source of information (ii) provides relevant information on organ weights and histopathology of reproductive organs. However, other reproductive tissues were not investigated in the study. In addtion, the study was conducted in animals that are not pregnant therefore it does not cover the other elements. Consequently, this study provides partially relevant information on aspect 1).

However, these sources of information have deficiencies affecting their reliability:

Reliability of information provided with the analogue substances

As explained in Section 1.1. of the Appendix common to several requests, you have not demonstrated that you reliably can predict the properties of the Substance by using test results obtained with analogue substances.

Results obtained from study (ii) not comparable to OECD TG 421

Investigations/specifications in a screening for reproductive/developmental toxicity study (OECD TG 421) include that sexual function and fertility shall be investigated in all animals of the parental generation; and each group should have at least 12 animals per dose group.

In study (ii), the following specifications are not to the requirements of OECD TG 421 as the study was conducted with 10 animals/sex/dose group. However, histopathology has only been conducted on 5 animals per dose group. In addition, there are no results on reproductive tissues other than gonads.

Based on the above, the reliability of the contribution of the results obtained from this study to the weight of evidence is limited. The lower statistical power of the study introduce uncertainty in the results which must be considered.

Aspect 2) toxicity to the offspring

Information on pre- and peri-natal developmental toxicity reflected by litter sizes, postimplantation loss (resorptions and dead foetuses), stillborns, and external malformations, postnatal developmental toxicity reflected by survival, clinical signs and body weights of the pups (or litters), and other potential aspects related to pre-, peri- and postnatal developmental toxicity observed up to postnatal day 13.

The source of information (i) provides relevant information on toxicity to the offspring in the F1 generation.

The source of information (ii) was conducted in adult animals and does not provide information on the toxicity to offspring. Consequently, the study does not provide relevant information on aspect 2).

However, these sources of information have a deficiency affecting their reliability.

Specifically, the reliability issue related to read-across identified for aspect 1) applies equally to this aspect.

Aspect 3) systemic toxicity

Information on systemic toxicity include clinical signs, survival, body weights, food consumption, clinical biochemistry, and other potential aspects of systemic toxicity in the parental generation up to postnatal day 13.

The source of information (i) provides relevant information on aspect 3).

The source of information (ii) has investigated systemic toxicity in adult non-pregnant animals. However, the study does not cover clinical biochemistry. In addition, the study was conducted in animals that are not pregnant therefore it does not cover the elements of systemic toxicity for females up to postnatal day 13. Consequently, the study provides partially relevant information on aspect 3) for the P generation.

However, these sources of information have a deficiency affecting their reliability.

Specifically, the reliability issue related to read-across identified for aspect 1) applies equally to this aspect.

Conclusion on the weight of evidence

As indicated above, therere are sources of information relevant for the information requirement. However, the reliability of this infromation is hampered by the use of read-across and issues related to how the results were obtained in the studies which increases the uncertainty of the conclusion for the Substance. In addition, as explained in the Annex common to several requests, you have not provided adequate documentation addressing how you integrate the evidence to reach a robust conclusion on the weight of evidence.

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

Based on the above, your adaptation is rejected and the information requirement is not fulfilled.

Your comments on the draft decision are addressed in section 1 of the Appendix on Reasons common to several requests above.

3.3. Specification of the study design

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

4. Short-term toxicity testing on fish

Short-term toxicity testing on fish is an information requirement under Annex VIII to REACH (Section 9.1.3.).

4.1 Information provided for the information requirement

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

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

i. an OECD TG 203 key study conducted with source substance Nonan-1-ol (EC No. 205-583-7, CAS No. 143-08-8)
ii. USEPA 1975 test method supporting study conducted with source substance Nonan-1-ol (EC No. 205-583-7, CAS No. 143-08-8)
iii. a non-guideline supporting study conducted with source substance Nonan-1-ol (EC No. 205-583-7, CAS No. 143-08-8)

4.2 Assessment of the information provided

As explained in the Appendix on general considerations your adaptation is rejected.

On this basis, the information requirement is not fulfilled.

Your comments on the draft decision are addressed in section 2 of the Appendix on Reasons common to several requests above.

4.3 Study design

OECD TG 203 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.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 under Annex IX to REACH.

1.1. Information provided for the information requirement

You have adapted this information requirement by using Weight of evidence based on the following experimental data with substances other than the Substance:

i. Combined Repeat dose and Reproductive/Developmental Toxicity Screening Test (1992) conducted with dodecan-1-ol, EC No. 203-982-0.
ii. Sub-chronic toxicity study (90 days; 1966) conducted with hexan-1-ol, CAS No. 111-27-3.

1.2. Assessment of the information provided

You have adapted this information requirement using weight of evidence under Annex XI, Section 1.2.

As explained under Appendix on Reasons common to several requests, 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 8.6.2. at Annex IX includes similar information that is produced by the OECD TG 408. The following aspects of systemic toxicity are covered: 1) in-life observations, 2) blood chemistry, 3) organ and tissue toxicity.

We have assessed the individual sources of information with regard to relevance and identified the following issue(s):

Aspect 1) in-life observations

In-life observations must include information on survival, body weight development, clinical signs, functional observations, food/water consumption and other potential aspects of in life observations on the relevant physiological systems (circulatory, digestive/excretory, integumentary, musculoskeletal, nervous, renal/urinary, and respiratory).

The sources of information (i) and (ii) provide relevant information on aspect 1).

However, these sources of information have deficiencies affecting their reliability:

Reliability of information provided with the analogue substances

As explained in Section 1.1. of the Appendix common to several requests, you have not demonstrated that you reliably can predict the properties of the Substance by using test results obtained with other substances.

Results obtained from study (i) and (ii) not fully reliable when compared to the OECD TG 408

Investigations/specifications in a sub-chronic toxicity study (OECD TG 408) include:

a. Dosing of the Substance daily for a minimum of 90 days.
b. At least 10 male and 10 female animals for each test and control group. Full histopathology as specified in paragraphs 47-49 of the test guideline.

In study (i), the following investigations/specifications are not to the requirements of OECD TG 408:

a. the study has an exposure duration of 41-54 days.

In study (ii), the following investigations/specifications are not to the requirements of OECD TG 408:

b. the study had 10 animals/sex and dose group; however, histopathology has only been examined in 5 animals/sex and dose group

Based on the above, the reliability of the contribution of the results obtained from this study to the weight of evidence is limited. The lower statistical power and shorter exposure duration of the studies introduce uncertainty in the results which must be considered. This condition of exposure is essential because the effects observed over the longer exposure might be considerably more pronounced over a shorter study duration.

Aspect 2) blood chemistry

Information on blood chemistry must include haematological (full-scale) and clinical chemistry analysis (full-scale), and other potential aspects related to blood chemistry to address relevant physiological systems (circulatory digestive/excretory, endocrine, immune, musculoskeletal, and renal/urinary).

The sources of information (i) and (ii) provide relevant information on aspect 2).

However, these sources of information have a deficiency affecting their reliability. Specifically, the reliability issue related to read-across, low statistical power and shorter exposure duration identified for aspect 1) applies equally to this aspect.

Aspect 3) organ and tissue toxicity

Organ and tissue toxicity must include information on terminal observations on organ weights, gross pathology and histopathology (full-scale) and other potential aspects related to organ and tissue toxicity to address relevant physiological systems (circulatory, digestive/excretory, endocrine, immune, integumentary, musculoskeletal, nervous, renal/urinary system, reproductive, and respiratory).

The source of information (i) provides relevant information on aspect 3).

The source of information (ii) has not investigated all the elements of aspect 3); histopathology of thymus, peripheral nerve, muscle, spinal cord, eye plus optic nerve, pituitary or trachea are missing. Consequently, it provides partly relevant information on aspect 3).

However, these sources of information have deficiencies affecting their reliability:

Specifically, the reliability issues related to read-across, low statistical power and shorter exposure duration identified for aspect 1) apply equally to this aspect.

Conclusion on the weight of evidence

As indicated above, there are sources of information (partially) relevant for the information requirement. However, the reliability of this infromation is hampered by the use of read-across and issues related to how the results were obtained in the studies which increases the uncertainty of the conclusion for the Substance. In addition, as explained in the Annex common to several requests, you have not provided adequate documentation addressing how you integrate the evidence to reach a robust conclusion on the weight of evidence.

Therefore, it is not possible to conclude, based on any source of information alone or together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 408 study.

Based on the above, your adaptation is rejected and the information requirement is not fulfilled.

Your comments on the draft decision are addressed in section 1 of the Appendix on Reasons common to several requests above.

1.3. Information on 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 of the Substance; Guidance on IRs and CSA, Section R.7.5.6.3.2.

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

Therefore, the 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.

2.1 Information provided for the information requirement

You have adapted this information requirement by using Weight of evidence based on the following experimental data with other substances than the Substance:

(i) Pre-natal developmental toxicity study (1997) in rats conducted with the analogue substance octan-1-ol, EC No. 203-917-6
(ii) Sub-chronic toxicity study (90 days; 1966) conducted with hexan-1-ol, CAS No. 111-27-3 provided for the DNEL derivation.

2.2 Assessment of the information provided

You have adapted this information requirement using weight of evidence under Annex XI, Section 1.2.

As explained under Appendix on Reasons common to several requests, 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 aspects are covered: 1) prenatal developmental toxicity, 2) maternal toxicity, and 3) maintenance of pregnancy.

We have assessed the individual sources of information with regard to relevance and identified the following issue(s):

Aspect 1) pre-natal developmental toxicity

Pre-natal developmental toxicity includes information after pre-natal exposure on embryonic/foetal survivial (number of live foetuses; number of resorptions and dead foetuses,

postimplantation loss), growth (body weights and size) and structural malformations and variations (external, visceral and skeletal).

The source of information (i) provides relevant information on aspect 1).

The source of information (ii) was conducted in adult animals and does not provide information on the toxicity to offspring. Consequently, the study does not provide relevant information on aspect 1).
In addition, these sources of information have deficiencies affecting their reliability:

Reliability of read-across predictions

As explained in Section 1.1. of the Appendix common to several requests, you have not demonstrated that you reliably can predict the properties of the Substance by using test results obtained with analogue substances.

Results obtained from study (ii) is not fully reliable when compared to the OECD TG 414

Investigations/specifications in a pre-natal developmental toxicity study (OECD TG 414) include that each group should aim to have 20 female animals with implantation sites at necropsy. Groups with fewer than 16 animals with implantation sites may be inappropriate.
In study (ii), the following investigations/specifications are not to the requirements of the OECD TG 414 as the study started with 8-10 animals per group.

Based on the above, the reliability of the contribution of the results obtained from this study to the weight of evidence is limited. The lower statistical power the study introduce uncertainty in the results which must be considered.

Aspect 2) maternal toxicity and aspect 3) maintenance of pregnancy

Maternal toxicity includes information after gestational exposure on maternal survival, body weight and clinical signs and other potential aspects of maternal toxicity in dams.

Maintenance of pregnancy includes information on abortions and/or early delivery as a consequence of gestational exposure and other potential aspects of maintenance of pregnancy.

The source of information (ii) was conducted in adult animals and does not provide information on the toxicity to offspring. Consequently, the study does not provide relevant information on aspects 2) and 3).

The sources of information (i) provides relevant information on aspects 2) and 3).

However, this source of information has a deficiency affecting its reliability. Specifically, the reliability issue related to read-across identified for aspect 1) above also applies equally to this aspect.

Conclusion on the weight of evidence

As indicated above, while there are sources of information (partially) relevant for the information requirement, the reliability of this information is hampered by the use of read-across and issues related to how the results were obtained in the studies which increases the uncertainty of the conclusion for the Substance. In addition, as explained in the Annex common to several requests, you have not provided adequate documentation addressing how you integrate the evidence to reach a robust conclusion on the weight of evidence.

Therefore, it is not possible to conclude, based on any source of information alone or together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 414 study.

Based on the above, your adaptation is rejected and the information requirement is not fulfilled.

Your comments on the draft decision are addressed in section 1 of the Appendix on Reasons common to several requests above.

2.3 Information on study design

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.

3. Long-term toxicity testing on aquatic invertebrates

Long-term toxicity testing on aquatic invertebrates is an information requirement under Annex IX to REACH (Section 9.1.5.).

3.1 Information provided for the information requirement

You have provided a QSAR prediction for long-term toxicity on aquatic invertebrates using the model for chronic aquatic toxicity of long-chain alcohols (2009, Schäfers et al.)

3.2 Assessment of the information provided

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

Assessment of your (Q)SAR adaptation

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

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

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

Under ECHA Guidance R.6.1.7.3. a prediction is adequate for the purpose of classification and labelling and/or risk assessment if the following cumulative conditions is/are met:

- the composition of the substance is clearly defined, and
- different constituents of the same substance are predicted individually.

Your registration dossier provides the following information:

- In Section 1.1 of your technical dossier, you define the Substance as UVCB;
- In Section 1.2, you indicate the following constituents in the composition of your Substance: Nonan-1-ol (EC 205-583-7, CAS 143-08-8), 2-methyloctan-1-ol (EC 212-457-5, CAS 818-81-5), 2-ethylheptan-1-ol (EC 212-444-4, CAS 817-60-7), and 2-propylhexan-1-ol (EC 212-443-9, CAS 817-46-9);
- For the assessment, you provided predictions for the following structure: Nonan-1-ol

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

(EC 205-583-7, CAS 143-08-8).

As you have used only one structure for the prediction while the Substance is composed of four constituents you have not covered all constituents of the Substance.

You have not demonstrated that the prediction is adequate for the purpose of classification and labelling and/or risk assessment and the cumulative conditions of Annex XI, section 1.3. are not met.

Therefore, the information requirement is not fulfilled.

Your comments on the draft decision are addressed in section 2 of the Appendix on Reasons common to several requests above.

3.3 Study design

OECD TG 211 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.2.

4. 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.).

4.1 Information provided for the information requirement

You have provided a justification to omit the study which you consider to be based on Annex IX, Section 9.1., Column 2. In support of your adaptation, you did not provide any justification.

4.2 Assessment of the information provided

We have assessed this information and identified the following issue:

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).

Your adaptation is therefore rejected. On this basis, the information requirement is not fulfilled.

Your comments on the draft decision are addressed in section 2 of the Appendix on Reasons common to several requests above.

4.3 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.).

OECD TG 210 specifies that for difficult to test substances OECD GD 23 must be followed. As already explained above, the Substance is difficult to test. Therefore, you must fulfil the requirements described in 'Study design' under Appendix A.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[9].

B. Test material

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 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 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.

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 E: 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 F: 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 05 January 2021.

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

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

Comments on the deadline to submit the requested information in this decision

In your comments you requested an extension of the deadline for providing the requested information from 24 months to 45 months. You argue that the extension is needed to perform sufficient studies to support read-across the toxicity information requirements of the larger category of C6-C24 alcohols of which the Substance is a member. In response, ECHA notes the following.

Your read-across testing strategy as explained in your comments refers to conducting tests on substances which are not addressed by this compliance check decision. In addition, the testing strategy covers information requirements which are not within the scope of this compliance check. However, for the calculation of the deadline ECHA can only take into account the requests in this decision.

Therefore, an extension of the deadline set in the decision to accommodate your intention to conduct a tentative testing strategy which may or may not result in compliance for the Substance is not considered justified.

The deadline set in this decision allows for generating the required data on the Substance as a result of incompliances identified in your registration. This deadline has already been set to allow sequential testing where appropriate.

ECHA took into account your comments and did not amend the deadline.

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 G: 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 H: 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]

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.