Helsinki, 01 September 2020

Addressees
Registrants of Isopropyl nitrate listed in the last Appendix of this decision

Date of submission for the jointly submitted dossier subject of this decision
18/05/2018

Registered substance subject to this decision, hereafter 'the Substance'
Substance name: Isopropyl nitrate
EC number: 216-983-6
CAS number: 1712-64-7

Decision number: [Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/D)]

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (REACH), ECHA requests that you submit the information listed below by the deadline of ***8 September 2021***.

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

A. Requirements applicable to 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: Bacterial reverse mutation test, EU B.13/14. /OECD TG 471)

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

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

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

3. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method EU C.2./OECD TG 202);

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

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

B. Requirements applicable to 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. *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or OECD TG 490), only if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained;

3. Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.; test method EU B.7./OECD 407) in rats, oral route;

4. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method OECD 421/422, in rats, oral route.

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

6. Hydrolysis as a function of pH (Annex VIII, Section 9.2.2.1.; test method OECD TG 111).

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

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". 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.

Approved[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

(i) Assessment of the Grouping of substances and read-across approach, in light of the requirements of Annex XI, Section 1.5.

You seek to adapt the following standard information requirements by 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.)

ECHA has considered the scientific and regulatory validity of your 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. 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[2] and related documents[3, 4].

A. Predictions for properties

a. Prediction for toxicological properties

You have provided the following reasoning for the prediction of toxicological properties (in the IUCLID section 7.6.1):
"*The presence in the molecule of a substance of the nitrogen atom associated with double bond oxygen almost always determines the toxicity of the compound. The reason most likely is that substances of this nature are easily recovering, i.e. they release oxygen and are strong oxidants. Therefore, all such compounds, such as nitro compounds R-NO2, nitroso compounds R-NO, nitric acid esters - nitrites RO-NO and nitric acid esters - nitrates RO-NO2, - substantially affect the organism in an analogous way destroy hemoglobin in the blood by oxidizing it to methaemoglobin. In addition, their poisonous effect is manifested in all the cells and tissues of the body.*

Pentaerythritol Tetranitrate is the lipid soluble polyol ester of nitric acid belonging to the family of nitrovasodilators that exhibit vasodilatory property. Pentaerythritol tetranitrate releases

[2] Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of Chemicals. 2008 (May) ECHA, Helsinki. 134. pp. Available online: https://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf/77f49f81-b76d-40ab-8513-4f3a533b6ac9
[3] 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)
[4] 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

free nitric oxide (NO) after denitration reaction, which triggers NO-dependent signaling transduction involving soluble guanylate cyclase (sGC). NO binds reversibly to the ferrous-heme center of sGC, thereby causes conformational change and activates the enzyme. Activation results in increasing cellular levels of cyclic guanosine monophosphate (cGMP) within vascular smooth muscle, which results in vasodilation mediated by cGMP-dependent protein kinases. Furthermore, this agent causes arterial and venous bed dilation in a dose-dependent manner.

Considering the fact that both PETN and Isopropyl nitrate are esters with nitric acid, we assume that the available data on genetic toxicity of PETN is valid also for Isopropyl nitrate."

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 qualitatively and quantitatively equal to those of the source substance.

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

Missing supporting information on the target substance

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.

Supporting information must include bridging studies to compare properties of the category members and to support your prediction, which is based on similarity of the relevant toxic properties.

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

The data set reported in the technical dossier does not include relevant, reliable and adequate information for *both* the Substance and of the source substance to support your read-across hypothesis. More notably, you have not provided any genotoxicity toxicity studies for the target substance, which could be considered as bridging studies to demonstrate toxicological similarity between the source and target substance. Furthermore, you have not provided a comparison of the physico-chemical properties and lower tier toxicity endpoints to confirm that both substance cause the same type of effects.

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

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

Missing information on the formation of common compound

As indicated above, your read-across hypothesis is based on the transformation of the Substance and of the source substance to a common compounds. In this context, information characterising the rate and extent of the break-down of the Substance and of the source substance(s) is necessary to confirm the formation of the proposed common break-down product and to assess the impact of the exposure to the parent compounds.

You have not provided any experimental data, neither about the break-down of your the Substance nor about the break-down of the source substance.

In the absence of this information, you have not provided supporting evidence establishing that the proposed common break-down products are formed as assumed in your read-across hypothesis. 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, your adaptation does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. Therefore, your adaptation is rejected and it is necessary to perform testing on your Substance.

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

1. *In vitro* gene mutation study in bacteria (Annex VII, Section 8.4.1.)

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

You have adapted the provided information under the rules set out in Annex XI, Section 1.5.

You have provided a key study in your dossier:

i. Ames test OECD TG 471 with analogue/source substance Pentaerithrityl tetranitrate EC No. 201-084-3, in 1989, with the following strains, TA 98, TA 100, TA 1535, TA and 1537.

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

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

Therefore, the information requirement is not fulfilled.

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

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

Skin sensitisation is a standard information requirement in Annex VII, Section 8.3. to the REACH Regulation. Column 1 of Section 8.3. requires the registrants to submit information allowing a conclusion whether the substance is a skin sensitiser and whether it can be presumed to have the potential to produce significant sensitisation in humans (Cat. 1A), and risk assessment, where required.

You have provided a QSAR modelling results, reliability 2, made with QSAR Toolbox.

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

Annex XI, Section 1.3. states that results obtained from valid QSAR models may be used instead of testing when the following cumulative conditions are met, in particular:

1. results are derived from a QSAR model whose scientific validity has been established;
2. the substance falls within the applicability domain of the QSAR model;
3. adequate and reliable documentation of the applied method is provided; and
4. the results are adequate for classification and labelling and/or risk assessment.

According to ECHA's Practical guide "How to use and report (Q)SARs", section 3.4, a QSAR Model Reporting Format (QMRF) and a QSAR Prediction Reporting Format (QPRF) are required to establish the scientific validity of the model, to verify that the Substance falls within the applicability domain of the model, and to assess the adequacy of the prediction for the purposes of classification and labelling.

Your interpretation of results is: "positive result for skin sensitisation". Your waiver and justification is: "No skin sensitisation is expected taking the prescribed safety measures". You have not classified the Substances for skin sensitisation, because according to you "data (is) lacking".

You have not provided sufficient documentation for the QSAR prediction. In particular, you have not included a QPRF in your technical dossier. Therefore, ECHA cannot establish whether the model is scientifically valid, whether the Substance falls within the applicability domain of the model, and whether the results are adequate for classification and labelling and/or risk assessment.

The adaptation you provided does not fulfil the criteria specified in Annex XI, Section 1.3., and it is therefore rejected.

Therefore, the information requirement is not fulfilled, and your conclusion that the Substance does not cause skin sensitisation is rejected.

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

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

You have provided a study summary for a QSAR prediction on substance isopropyl nitrite made with "ECOSAR: DAPHNID 48 h LC50 Mortality Aliphatic Amines".

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

Under Annex XI, Section 1.3, you may adapt the information requirement with a QSAR model provided you submit a scientifically-supported justification and fulfil the following criteria:
- the substance falls within the applicability domain of the QSAR model; and
- the results are adequate for classification and labelling and/or risk assessment.

Your dossier only contains a QSAR prediction as information for the endpoint.

You have reported a predicted 48h-EC50 of 2.74 mg/L using model "ECOSAR: DAPHNID 48 h LC50 Mortality Aliphatic Amines".

This prediction pertains to substance isopropyl nitrite.

A log Kow value of 1.79 has been used as input parameter for this prediction.

The log Kow reported for the Substance is 1.66.

However:

- Based on the information reported in your study summary, the prediction pertains to substance isopropyl nitrite, not to the Substance (isopropyl nitrate). A log Kow value of 1.79 has been used as input parameter for this prediction, whereas the log Kow reported for the Substance is 1.66. You have provided no explanations or justifications for this. That makes your prediction irrelevant for the information requirement and thus inadequate for classification and labelling and/or risk assessment.

- The model you have used, "ECOSAR: DAPHNID 48 h LC50 Mortality Aliphatic Amines", pertains to aliphatic amines. The Substance is not an aliphatic amine (nor is isopropyl nitrite). Therefore, the Substance (or isopropyl nitrite) is outside the applicability domain of that model.

Therefore, your adaptation is rejected, and the information requirement is not fulfilled.

To fulfil the information requirement, the following test method is considered suitable: OECD TG 202. When conducting the test, precautions should be taken to mitigate the volatilisation of the Substance.

4. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

Growth inhibition study aquatic plants is a standard information requirement in Annex VII to REACH.

You have provided a QSAR prediction using the QSAR Toolbox.

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

Under Annex XI, Section 1.3, you may adapt the information requirement with a QSAR model provided you submit a scientifically-supported justification and fulfil the following criteria:
- results are derived from a QSAR model whose scientific validity has been established;
- the substance falls within the applicability domain of the QSAR model;
- adequate and reliable documentation of the applied method is provided; and
- the results are adequate for classification and labelling and/or risk assessment.

You have reported a predicted 84h-EC50 of 41.4 mg/L.

You have used the QSAR Toolbox to collect toxicity data on algae for substances with mode of action "basesurface narcotics". This constituted the training set of your model. You have then predicted an EC50 calculated from the arithmetic mean of the toxicity values for the "nearest 5 neighbours", i.e. for the five substances having the log Kow values closest to the log Kow of the Substance.

However, you have not demonstrated that the substance falls within the applicability domain of your model:

- You have not provided the identity of the substances included in the training set. Therefore, it is not possible to assess directly the similarities between these substances and the applicability domain of your model. You have mentioned that the substances selected for the training set have a narcotic mode of action. This would only be acceptable if the Substance had merely a narcotic mode of action. However, you have provided no evidence to support such an assumption. If the Substance has a different mode of action, then it was outside the applicability domain of your model.

Furthermore, you have not established the scientific validity of your model:

- The toxicity values of the substances included in the training set range over nearly 6 orders of magnitude. This indicates that the substances in the training set have very different toxicities. The graph presented in the document attached to the study summary shows a very poor, if any, correlation between the toxicities and the log Kow values of the substances in the training set. This indicates that log Kow cannot explain the difference in toxicity values for the substances in the training set. You have not demonstrated the scientific rationale for a model that would attempt to link log Kow with the toxicities of the substances belonging to this training set.

- Your prediction was based only on the information from five substances, defined as the "nearest 5 neighbours" for the Substance. You have selected these five substances as those amongst the training set having the log Kow values closest to the log Kow of

the Substance. You have provided no justification for this approach. As explained above, log Kow does not explain the vast differences of toxicities between the substances in the training set: substances with similar log Kow values does not necessarily have similar toxicity values. The toxicity values for the five substances you have defined as the "nearest 5 neighbours" indeed range over more than 2 orders of magnitude even though their log Kow values range only from 1.34 to 2.01. Therefore, you have not demonstrated that these five substances can be regarded as similar. There is no scientific rationale for grouping these five substances as an attempt to predict the ecotoxicity of the Substance.

- You have predicted an EC50 value from the arithmetic mean of the values for the "nearest 5 neighbours" rather than from a regression line. This is consistent with the fact that log Kow is not a useful descriptor to explain the large disparities of the toxicity value amongst those substances. However, as explained in the previous point, these five substances cannot be regarded as similar. Therefore, there is no scientific rationale for this calculation.

Finally, the results obtained are regarded as not adequate for classification and labelling and/or for risk assessment:

- The interval reported for you prediction is extremely large: the 95% prediction interval ranges from 0.0942 to 1.82 10^4 mg/L. Therefore, your prediction is highly uncertain. It is as such not adequate for classification and labelling and/or for risk assessment.

Therefore, your adaptation is rejected, and the information requirement is not fulfilled.

To fulfil the information requirement, the following test method is considered suitable:
OECD TG 201. When conducting the test, precautions should be taken to mitigate the volatilisation of the Substance.

5. Ready biodegradability (Annex VII, Section 9.2.1.1.)

Ready biodegradability is a standard information requirement at Annex VII of REACH.

You have provided a QSAR prediction based on model Biowin1 from software EPISUITE (v.1.0).

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

Under Annex XI, Section 1.3, you may adapt the information requirement, provided you fulfil the identified criteria, and submit a scientifically-supported justification:
- results are derived from a QSAR model whose scientific validity has been established;
- the substance falls within the applicability domain of the QSAR model;
- adequate and reliable documentation of the applied method is provided; and
- the results are adequate for classification and labelling and/or risk assessment.

A QSAR prediction on its own cannot be used to adapt the information requirement according to Annex XI, Section 1.3 for this endpoint because it is not adequate for the purpose of classification and labelling. In general, no quantitative estimation method (QSAR) is sufficiently accurate to unequivocally predict rapid biodegradation. Results from such methods may only be used to predict that a substance is not rapidly degradable, or in a weight of evidence approach (see ECHA Guidance R.6, Section R.6.1.5; ECHA's Practical guide "*How to use and report (Q)SARs*", section 2.5; and ECHA Guidance R7b, Section R.7.9.4.1).

However, your dossier only contains a QSAR prediction as information for ready-biodegradability.

The model used predicts a biodegradability probability of 0.698. You concluded that the Substance was readily biodegradable.

You have claimed that "*the (Q)SAR used for the prediction has no applicability domain*".

However, the Biowin models do have applicability domains and it is possible to assess that the Substance does not fall within.

An appendix to the help file of the Biowin models lists the molecular fragments, as well as their maximum number of instances, present in the training sets of these models. The help file explicitly indicates that the users should check manually whether the substance for which the predictions are performed contains functional groups that are not represented in the training set of the models. Similar recommendations are given in ECHA Guidance R7b Section R.7.9.4.1 and in ECHA's Practical guide "*How to use and report (Q)SARs*", section 3.2).

The Substance is a nitrate ester. However, there is no occurrence of the nitrate group in the training sets of the Biowin models. Therefore, the Substance does not fall within the applicability domain of those models.

Therefore, the information provided is not appropriate to conclude on the ready biodegradability of the Substance.

Your adaptation is rejected, and the information requirement is not fulfilled.

To fulfil the information requirement, the following test methods are considered suitable: OECD TG 301C, OECD TG 301D, OECD TG 301F or OECD TG 310. When conducting the test, precautions should be taken to mitigate the volatilisation of the Substance.

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 (Annex VIII, Section 8.4.2.)

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 adapted this information requirement by using a Grouping of substances and read-across approach under Annex IX, Section 1.5.

You have provided a key study in your dossier:

i. Chromosome aberration test OECD TG 473**,** with analogue/source substance Pentaerithrityl tetranitrate EC No. 201-084-3, in 1989.

As explained in the Appendix on general considerations, your adaptation is rejected. Therefore, the information requirement is not fulfilled.

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. ***Only if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2. is obtained, In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or OECD TG 490), with the Substance;**

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.

For Annex VIII, 8.4.3., you have not provided any study in your dossier. However, you argued that this information requirement is not triggered because "*positive result was found in in vitro cytogenicity study in mammalian cells*". First, the results of the *in vitro* cytogenicity study was negative, and second, both *in vitro* genotoxicity studies, which you have provided are rejected due to the deficiencies of the read-across as specified above (Appendix A, Section 1, and B, Section 1). Therefore, ECHA disagrees with your argument that the *in vitro* gene mutation study in mammalian cells is not triggered.

We have further assessed the information you provided and identified the following issue(s):

Inadequate *in vitro* gene mutation test in bacteria and *in vitro* cytogenicity test

The adaptation using a read-across approach under Annex XI, Section 1.5 for the *in vitro* gene mutation test in bacteria and *in vitro* cytogenicity test provided in the dossier is rejected for the reasons provided in the Appendix on general considerations and section A.1 and B.1 above.

The result of the requests for information A.1 and B.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.

Therefore, the information requirement is not fulfilled.

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. Short-term repeated dose toxicity study (28 day), oral route (Annex VIII, Section 8.6.1.)

A Short-term repeated dose toxicity study (28 days) is a standard information requirement in Annex VIII to REACH.

You have provided a key study for this endpoint in your dossier:

> Chronic inhalation toxicity study with the Substance, made in 1967, reliability 1, no GLP, in rats, via inhalation, the dose varies from 0.2 to 0.3 mg/L; only one dose was administered.

You also have adapted this information according to Annex XI, Section 3 of REACH.

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

A. Inadequate study

Although you do not explicitly claim an adaptation, ECHA understands that the information provided was submitted in order to meet the required information by way of adaptation under Annex, Section XI 1.1.2. This adaptation rule enables registrants to claim that the data from experiments not carried out according to GLP or the test methods referred to in Article 13(3) can be considered equivalent to data generated by those test methods where a number of cumulative conditions are met, in particular:

Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3), in this case OECD TG 407, which include the following key parameters;

- testing of at least three dose levels and a concurrent control;
- examination of the animals for weight and histopathology (including thyroid gland/ thyroid hormone measurements)

The study you have provided:

- was conducted with less than three dose levels.
- did not include clinical chemistry, gross pathology and histopathology.

Therefore this study does not meet the requirements of OECD TG 407 and is rejected.

B. Annex XI, Section 3, (Substance-tailored exposure-driven testing)

As stated in Annex XI, Section 3, testing in accordance with Sections 8.6 and 8.7 of Annex VIII and in accordance with Annexes IX and X may be omitted based on the exposure scenario(s) developed in the CSR, by providing an adequate and scientifically-supported justification based on a thorough and rigorous exposure assessment in accordance with Section 5 of Annex I. Any one of the criteria of Section 3.2.(a),(b) or (c) shall be met. In particular:

1. the results of the exposure assessment covering all relevant exposures throughout

the life cycle of the substance demonstrate the absence of or no significant exposure in all scenarios of the manufacture and all identified uses as referred to in Annex VI section 3.5.
2. the comparison of the derived DNEL and PNEC with the results of the exposure assessment shows that exposures are always well below the derived DNEL or PNEC.

You argue that *"a short-term toxicity study does not need to be conducted because oral human exposure can be excluded."*

Your dossier includes a DNEL based on a repeated dose toxicity and several PROCs, including PROC 5, 8a, 9, 16 and 21. Your CSR does not provide risk characterisation ratios.

First, the PROC provided indicate potential for exposure and contradict the claim of highly unlikely exposure.

Second, in the absence of risk characterisation ratios, you have not documented that exposures are below the derived DNEL.

Therefore your adaptation is rejected.

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

Information on the design of the study to be performed

Referring to the criteria in Annex VIII, Section 8.6.1, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity, because the Substance is a liquid of very low vapour pressure and no uses with spray application are reported that could potentially lead to aerosols of inhalable size.

Therefore the sub-acute toxicity study must be performed according to the OECD TG 407, in rats and with oral administration of the Substance.

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

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 a QSAR prediction for this endpoint, using QSAR Toolbox.

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

Annex XI, Section 1.3. states that results obtained from valid QSAR models may be used instead of testing when the following cumulative conditions are met, in particular:

1. results are derived from a QSAR model whose scientific validity has been established;
2. the substance falls within the applicability domain of the QSAR model;
3. adequate and reliable documentation of the applied method is provided; and
4. the results are adequate for classification and labelling and/or risk assessment.

According to ECHA's Practical guide "How to use and report (Q)SARs", section 3.4, a QSAR Model Reporting Format (QMRF) and a QSAR Prediction Reporting Format (QPRF) are required to establish the scientific validity of the model, to verify that the Substance falls within the applicability domain of the model, and to assess the adequacy of the prediction for the purposes of classification and labelling.

You have reported that: "*No quantitative result was determined. Not known precedent reproductive and developmental toxic potential.*" You have also concluded the following: "*Q: RBA<0.00001% (Estrogen Binding Affinity(USA))*"

You have not provided sufficient documentation for the QSAR prediction. In particular, you have not included a QMRF and/or a QPRF in your technical dossier. Furthermore, you have indicated that "*the (Q)SAR used for the prediction has no applicability domain.*"

Therefore, ECHA cannot establish whether the model is scientifically valid, whether the Substance falls within the applicability domain of the model, and whether the results are adequate for classification and labelling and/or risk assessment.

The adaptation you provided does not fulfil the criteria specified in Annex XI, Section 1.3. and it is therefore rejected.

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[6] administration of the Substance.

5. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

Short-term toxicity testing on fish is a standard information requirement in Annex VIII to REACH.

You have provided a QSAR prediction, using the QSAR Toolbox.

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

Under Annex XI, Section 1.3, you may adapt the information requirement with a QSAR model provided you fulfil all the identified criteria, and submit a scientifically-supported justification:

- results are derived from a QSAR model whose scientific validity has been established;
- the substance falls within the applicability domain of the QSAR model;
- adequate and reliable documentation of the applied method is provided; and
- the results are adequate for classification and labelling and/or risk assessment.

You have reported a predicted 84h-EC50 of 34.1 mg/L.

You have used the QSAR toolbox to collect toxicity data, on algae, for substances with mode of action "basesurface narcotics". This constituted the training set of your model. You have then predicted an EC50 calculated from the arithmetic mean of the toxicity values for the "nearest 6 neighbours", i.e. for the six substances claimed to have the log Kow values closest to the log Kow of the Substance.

However, you have not demonstrated that the substance falls within the applicability domain of your model:

- You have not provided the identity of the substances included in the training set.

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

Therefore, it is not possible to assess directly the similarities between these substances and the applicability domain of your model. You have mentioned that the substances selected for the training set have a narcotic mode of action. This would only be acceptable if the Substance had merely a narcotic mode of action. However, you have provided no evidence to support such an assumption. If the Substance has a different mode of action, then it was outside the applicability domain of your model.

Furthermore, you have not established the scientific validity of your model:

- The information reported in the document attached to your study summary indicates that you have used toxicity data on algae whereas the information requirement is for toxicity to fish. Your prediction would thus pertain to algae, not to fish. You have provided no explanations or justifications for this.

- The toxicity values of the substances included in the training set range over nearly 6 orders of magnitude. This indicates that the substances in the training set have very different toxicities. The graph presented in the document attached to the study summary shows a very poor, if any, correlation between the toxicities and the log Kow values of the substances in the training set. The toxicity values range over nearly 6 orders of magnitude. This indicates that log Kow cannot explain these difference in toxicity values for the substances in the training set. You have not demonstrated the scientific rationale for a model that would attempt to link log Kow with the toxicities of the substances belonging to this training set.

- Your prediction was actually based only on the information from six substances, defined as the "nearest 6 neighbours" for the Substance. You have selected these six substances as those amongst the training set having the log Kow values closest to the log Kow of the Substance. You have provided no justification for this approach. As explained above, log Kow does not explain the huge differences of toxicities between the substances in the training set: substances with similar log Kow values does not necessarily have similar toxicity values. The toxicity values for the six substances you have defined as the "nearest 6 neighbours" indeed range over nearly 2 orders of magnitude even though their log Kow values range only from 1.45 to 1.89. Therefore, you have not demonstrated that these six substances can be regarded as similar. There is no scientific rationale for grouping these six substances as an attempt to predict the ecotoxicity of the Substance.

- You have predicted an EC50 value from the arithmetic mean of the values for the "nearest 6 neighbours" rather than from a regression line. This is consistent with the fact that log Kow is not a useful descriptor to explain the large disparities of the toxicity value amongst those substances. However, as explained in the previous point, these six substances cannot be regarded as similar. Therefore, there is no scientific rationale for this calculation.

Finally, the results obtained are regarded as not adequate for classification and labelling and/or for risk assessment:

- The interval reported for you prediction is extremely large: the 95% prediction interval ranges from 0.295 to 3.94 10^3 mg/L. Therefore, your prediction is highly uncertain. It is as such not adequate for classification and labelling and/or for risk assessment.

Therefore, your adaptation is rejected, and the information requirement is not fulfilled.

To fulfil the information requirement, the following test method is considered suitable: OECD TG 203. When conducting the test, precautions should be taken to mitigate the volatilisation of the Substance.

6. Hydrolysis as a function of pH (Annex VIII, Section 9.2.2.1.)

Hydrolysis as a function of pH is a standard information requirement at Annex VIII of REACH.

You have provided one study summary which mentions three distinct references:

- '*Hydrolytic decomposition of esters of nitric acids*'. John W. Baker, D. M. Easty publication (1952)
- '*The chemistry of nitrate esters*'. R Boschan, R. T. Merrow, P. W. Van Dolah publication (1955)
- '*TKinetics, products, reaction mechanisms, and atmospheric impact*' - Scientific Figure on ResearchGate. Unknown publication (2016)

Although you do not explicitly claim an adaptation, ECHA understands that the first two references were submitted in order to meet the required information by way of adaptation under Annex, Section XI 1.1.2.

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

Figure provided

To comply with this information requirement, the study provided must be an OECD TG 111 study.

In the study summary, you have provided a figure (2016) without any reference to a study or study results.

You have not demonstrated that the information provided was from an OECD TG 111 study while this information also has the same deficiencies as those described for the two other publications described below.

Therefore, the information provided is rejected.

Adaptation provided

Annex, Section XI 1.1.2. enables registrants to claim that the data from experiments not carried out according to GLP or the test methods referred to in Article 13(3) can be considered equivalent to data generated by those test methods where a number of cumulative conditions are met, in particular:

1. Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
2. Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3);
3. Adequate and reliable documentation of the study is provided;
4. Adequacy for the purpose of classification and labelling and/or risk assessment.

You have cited several publications for the same study summary. Two of them are old (from 1952 and 1955).

The information you have provided cannot be regarded as equivalent to OECD TG 111:

- As distinct references are mentioned, it is not clear what the origin of the information reported actually is.
- Important experimental details are not reported: e.g. the test duration, the test temperature(s), whether precautions were taken to avoid losses from volatilisation.
- You have reported a hydrolysis half-life of 8 months for the Substance at neutral conditions, but you have not explained how this value was calculated.
- A figure displaying the hydrolysis rate constants as a function of pH for the Substance as well as for isobutyl nitrate is attached to the study summary. From this figure a hydrolysis rate constant of c.a. 2.10^{-6} s^{-1} can be determined at pH 6.9. Assuming first-order kinetics, this corresponds to a hydrolysis half-life of only c.a. 4 days.
- This figure is from an unknown publication. The source and details of the data used to draw this figure are no specified.
- You have mentioned Pinol (CAS: 2437-97-0) as hydrolysis product for the Substance. This does not seem plausible considering that the structures of the Substance and of Pinol are very different.

The information you have provided lacks crucial experimental details. As such, it does not provide adequate and reliable documentation and thus is not equivalent to a result generated by OECD test guideline 111.

Furthermore, the information reported in the study summary is conflicting for the hydrolysis rate or the hydrolysis half-life. It is likely incorrect for the identity of the hydrolysis product(s). Therefore those results and your conclusions are not reliable.

Therefore, the information requirement is not fulfilled and you must perform a hydrolysis study.

To fulfil the information requirement, the following test method is considered suitable:
OECD TG 111. When conducting the test, precautions should be taken to mitigate the volatilisation of the Substance.

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

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[7].

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 and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[8].

[7] https://echa.europa.eu/practical-guides
[8] https://echa.europa.eu/manuals

Appendix D: 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 18 June 2019.

The decision making followed the procedure of Articles 50 and 51 of REACH, as described below:

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

ECHA did not receive any comments by the end of the commenting period.

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix E: List of references - ECHA Guidance[9] 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)[10]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[10]

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[11]
Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

[9] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[10] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[11] 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 F: List of the registrants to which the decision is addressed and the corresponding information requirements applicable to them

Registrant Name	Registration number	(Highest) Data requirements to be fufilled
[redacted]	[redacted]	[redacted]

Note: where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas the decision is sent to the actual registrant.