EUROPEAN CHEMICALS AGENCY

~~Confidential~~

Helsinki, 15 January 2021

Addressees
Registrants of JS_99-97-8_[redacted] as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
10 December 2014

Registered substance subject to this decision ("the Substance")
Substance name: N,N-dimethyl-p-toluidine
EC number: 202-805-4
CAS number: 99-97-8

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 ***22 April 2022***.

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

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

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

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

Reasons for the requests are explained in the following appendices:

- Appendix entitled "Reasons common to several requests";
- Appendices entitled "Reasons to request information required under Annexes VII to X 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". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

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

Appendix on Reasons common to several requests

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

You seek to adapt the following standard information requirements by applying a weight of evidence approach in accordance with Annex XI, Section 1.2:

- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2)
- In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3)

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

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

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

However, for each relevant information requirement, you have not submitted any explanation why the sources of information provide sufficient weight of evidence leading to the conclusion/assumption that the Substance has or has not a particular dangerous property. Furthermore, you did not provide such an explanation of the weight of evidence conclusion in your comments to the draft decision.

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

1. Reliability of the read across approach

You have used sources of information relating to analogue substances submitted under your weight of evidence adaptations, for the following standard information requirements:

- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

In your comments on the draft decision, you provided further sources of information concerning analogue susbtances for the following standard information requirements:

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

ECHA has considered the scientific and regulatory validity of your grouping and read-across approach in general before assessing the specific standard information requirements in the following appendices.

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[2,3].

A. Predictions for ecotoxicological properties

You provided the following reasoning for the prediction of aquatic toxicity in your registration dossier: *"properties are similar and are comparable as a result of structural similarity"*. You have provided an updated read-across justification document in your comments on the draft decision. In this document you added the following reasoning: *'The overall common alerts in predicted structure-activity confirm the hypothesis that the target and read across analogues have similar reactivities towards biological targets.'*

You read-across between the structurally similar substances, N,N-dimethylaniline, EC No. 204-493-5 (CAS No. 121-69-7) as source substance and the Substance as target substance. In your comments on the draft decision you have added source substances toluene (EC 203-625-9) and N-methyl-N-phenylformamide (EC 202-262-3).

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 prediction of aquatic toxicity:

A. Read-across hypothesis

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

Your read-across hypothesis is that the similarity in chemical structure and in some of the physicochemical and ecotoxicological properties between the source substance(s) and the Substance is a sufficient basis for predicting the properties of the Substance for other endpoints. In addition, in your comments on the draft decision, you provide

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

a justification that the target and source substances share similar structural alerts using the OECD (Q)SAR Toolbox v.3.4.

However, Similarity in chemical structure and similarity of some of the physicochemical and ecotoxicological properties does not necessarily lead to predictable or similar ecotoxicological properties in other endpoints. As described above, a well-founded hypothesis is needed to establish a reliable prediction for a ecotoxicological property, based on recognition of the structural similarities and differences between the source substance(s) and the Substance.

Concerning the use of the OECD (Q)SAR Toolbox v.3.4, this does not provide a well-founded hypothesis, based on recognition of the structural similarities and differences between the source substances and the Substance.

Furthermore, the source substances toluene (EC 203-625-9) and N-methyl-N-phenylformamide (EC 202-262-3) are not sufficiently similar in chemical structure to the target substance, because they do not contain the N,N-dimethylbenzene moiety that distinguishes the target substance. Therefore read-across is not reliable.

A. *Adequacy and reliability of source studies*

A study summary must be provided covering sufficient information to make an independent assessment of the study, including a description of the study design and procedure and the test results.

However, the study summaries you provided do not cover this critical information, including for the studies on the additional sources substances toluene (EC 203-625-9) and N-methyl-N-phenylformamide (EC 202-262-3) added in your comments on the draft decision.

Therefore, it is not possible to make an independent assessment of the studies.

B. Predictions for toxicological properties

In the read-across justification document submitted with your comments on the draft decision, you extended your weight-of-evidence adaptation by providing further sources information, namely studies perfomed on analogue substances for the following standard information requirements:

- Read-across of *in vitro* gene mutation study in mammalian cells from the source substance toluene (EC 203-625-9).
- Read-across of screening for reproductive/developmental toxicity 3-methylaniline (EC 203-583-1) and 1-tert-Butyl-4-methylbenzene (EC 202-675-9).

In this document, you have provided the following reasoning for the prediction of toxicological properties: *'The overall common alerts in predicted structure-activity confirm the hypothesis that the target substance and the read-across analogues have similar reactivities towards biological targets.'*

ECHA understands that you predict the properties of the Substance relating these information requirements by 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:

A. Read-across hypothesis

As explained above, a read-across hypothesis needs to be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable.

However, your justification that the target and source substances have a common structure does not provide a well-founded hypothesis, based on recognition of the structural similarities and differences between the source substances and the Substance.

Furthermore, the source substances toluene (EC 203-625-9), 3-methylaniline (EC 203-583-1) and 1-tert-Butyl-4-methylbenzene (EC 202-675-9) are not sufficiently similar in chemical structure to the target substance, because they do not contain the N,N-dimethylbenzene moiety that distinguishes the target substance. Therefore read-across is not reliable.

B. 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*"[4]. The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s).

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 substance 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).

However, In your read-across justification you only provide a general statement referring to the toxicological properties for "*acute exposure*", "*irritation and sensitisation*", "*in vitro genetic toxicity*" and "*repeated dose toxicity*" for the Substance and the source substance(s). Morever, you did not provide a data matrix including relevant, reliable and adequate information for the Substance and the source substance(s) to allow the comparsion between the Substance and the source substances. For example for the mutagenicity data you only provide information for an *in vitro* gene mutation in mammalian cells with one of the analogue substances; you do not provide any information on the *in vitro* gene mutation in bacterial cells and *in vitro* chromosomal aberration in mammalian cells with the source substances.

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

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

C. *Relevance of the supporting information*

According to the ECHA Guidance[5] "*it is important to provide supporting information to strengthen the rationale for the read-across approach. Thus, in addition to the property/endpoint being read-across, it is also useful to show that additional properties, relevant to the endpoint, are also (qualitatively or quantitatively) similar between the source and target chemicals*".

In order to support your claim that your Substance and source substance(s) have similar properties for the endpoints under consideration in the read-across approach, you refer to their acute toxicity, irritation and sensitisation properties.

Whilst this information is pertinent to assess whether the substances may have similar properties for acute toxicity, irritation and sensitisation, these studies do not inform on the mutagenicity, and reproductive toxicity properties of the target and source substances. Accordingly, these information are not considered as relevant to support prediction of all the endpoints under consideration.

2. Reliability of the QSAR information

You have used QSAR prediction as sources of information submitted under your weight of evidence adaptations for the following standard information requirements:

- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)

ECHA notes the following shortcoming with regards to your QSAR adaptations:

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) (ECHA Guidance R.6.1.9. and R.6.1.10., respectively) 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 provided estimated ecotoxicity values for the endpoints derived using ECOSAR v1.1 and from the US EPA High Production Volume Information System (HPVIS) modelling system with the EPIWin Modeling Program. You have provided the outcome of the predictions. However, you have not provided documentation establishing the scientific validity of the model for the QSAR predictions (i.e. QMRF and QPRF are not provided in the technical dossier, including identity of the compounds used during the parameterisation of the models, defined descriptor and structural fragment domains) (ECHA Guidance R.6.1.5.). Furthermore, you did not provide this information in your comments on the draft decision.

Therefore, the QSAR predictions are not considered reliable, because it can not be established whether the (Q)SAR models are scientifically valid and/or that the Substance falls within the applicability domain of the prediction models.

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

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

1. Short-term toxicity testing on aquatic invertebrates

Short-term toxicity testing on aquatic invertebrates is an information requirement under Annex VII to REACH (Section 9.1.1.).

You have provided an adaptation under Annex XI, Section 1.2. of REACH (weight of evidence) with the following supporting information:

(i) a calculation of acute toxity to Daphnia from the HPVIS modelling system ([redacted], 1999);
(ii) a QSAR prediction from ECOSAR v1.1, 2012;
(iii) a read-across adaptation based on an analogue approach with the source substance N,N-dimethylaniline (EC No. 204-493-5).

In your comments on the draft decision you have included the following additional supporting information for the weight of evidence adaptation:

(iv) a read-across adaptation based on an analogue approach with the source substance toluene (EC 203-625-9);
(v) a read-across adaptation based on an analogue approach with the source substance N-methyl-N-phenylformamide (EC 202-262-3).

Based on the presented sources of information, you argue that the available data gives sufficient information to conclude on short-term toxicity on aquatic invertebrates and you state: *"By applying weight of evidence approach to the studies above, the EC50 value is expected to be in range of 13.7 to 23.758 mg/l"*.

To fulfil the information requirement, normally a study performed according to 202 must be provided. OECD TG 202 requires to investigate the following key investigation: the concentration leading to 50% immobilisation of daphnids at the end of the test.

The sources of information (i) to (v) provide relevant information on short-term toxicity on aquatic invertebrates. However, the reliability of these source of information to inform on the properties of the Substance is significantly affected by the following deficiencies:

A. Concerning sources of information (i) and (ii) the QSAR predictions are not considered reliable as explained in section 1.2 of the Appendix on Reasons common to several requests.

B. Concerning source of information (iii) to (v) you have not established that relevant properties of the Substance can be predicted from data on the analogue substance, as explained in section 1.1 of the Appendix on Reasons common to several requests.

The issues affecting the reliability of the sources of information are so significant that it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous property foreseen to be investigated in an OECD 202 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

2. Growth inhibition study aquatic plants

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

You have provided an adaptation under Annex XI, Section 1.2. of REACH (weight of evidence) with the following supporting information:

(i) a calculation of algal toxicity from the HPVIS modelling system ([redacted], 1999);
(ii) a QSAR prediction from ECOSAR v1.1, 2012;
(iii) a read-across adaptation based on an analogue approach with the source substance N,N-dimethylaniline (EC No. 204-493-5).

In your comments on the draft decision you have included the following additional supporting information for the weight of evidence adaptation:

(iv) a read-across adaptation based on an analogue approach with the source substance toluene (EC 203-625-9);
(v) a read-across adaptation based on an analogue approach with the source substance N-methyl-N-phenylformamide (EC 202-262-3).

Based on the presented sources of information, you argue that the available data gives sufficient information to conclude on growth inhibition on algae and you state: "*By applying weight of evidence approach to the studies above it can be observed that EC50 value is expected to be in range of 15.481 to 24.37 mg/l in 72 hrs to 96 hrs study on the basis of growth rate*".

To fulfil the information requirement, normally a study performed according to 201 must be provided. OECD TG 201 requires to investigate the following key investigations: the concentrations of the test material leading to a 50 % and 0% (or 10%) inhibition of growth at the end of the test. Growth must be expressed as the logarithmic increase in biomass (average specific growth rate) during the exposure period.

The sources of information (i) to (v) provide relevant information on growth inhibition on algae. However, the reliability of these source of information to inform on the properties of the Substance is significantly affected by the following deficiencies:

A. Concerning sources of information (i) and (ii) the QSAR predictions are not considered reliable as explained in section 1.2 of the Appendix on Reasons common to several requests.

B. Concerning source of information (iii) to (v), you have not established that relevant properties of the Substance can be predicted from data on the analogue substance, as explained in section 1.1 of the Appendix on Reasons common to several requests.

The issues affecting the reliability of the sources of information are so significant that it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous property foreseen to be investigated in an OECD 201 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

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

1. In vitro gene mutation study in mammalian cells

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

Triggering of the study

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

Information in the dossier and the comments to the draft decision

You have provided an adaptation under Annex XI, Section 1.2. of REACH (weight of evidence) with the following supporting information with the Substance:

(i.) *in vitro* gene mutation study in bacteria (Taningher *et al.*, 1993)
(ii.) *in vitro* gene mutation study in bacteria ([redacted], 2012)
(iii.) *in vitro* gene mutation study in bacteria (US EPA, 2012)
(iv.) *in vitro* cytogenicity / chromosome aberration study in mammalian cells based on QSAR prediction ([redacted], 2012)
(v.) *in vivo* cytogenicity / chromosome aberration study in mammalian cells ([redacted], 2012)

In your comments to the draft decision you additionally provided the following information with the Substance:

(vi.) *In vitro* mammalian cell gene mutation tests using the thymidine kinase gene [redacted] 2002)
(vii.) *In vivo* Comet assay in rats and mice ([redacted], 2018)
(viii.) *In vivo* alkaline DNA elution assay ([redacted] 1993)

You also provided the following study with the analogue substance toluene (EC no. 203-625-9)

(ix.) *In vitro* mammalian cell gene mutation tests using the thymidine kinase gene ([redacted] 1988)

In your comments to the draft decision you have also concluded that based on the sources of information provided "*the classification for Genetic toxicity has been changed from No Classification to "H341: Suspected of causing genetic defects' which comprises heritable genetic damage as well as somatic cell mutagenicity*"". You further indicate that the Substance "*has been proved to be carcinogenic, and it is registered as Category 1B*". We understand with this comment that you are invoking an adaptation under Column 2 of Section 8.4.3, Annex VIII to REACH.

A. Weight of evidence adaptation

To fulfil this information requirement, normally a study performed according to OECD TG 476 or 490 must be provided. OECD TG 476 or 490 requires to investigate, in mammalian cells, 1) the cytotoxicity and 2) the frequency of gene mutations (mutant frequency) in the same study.

As explained in the Appendix on Reasons common to several requests we assessed this information and identified the following issues:

1) Cytotoxicity

Sources of information i. to iv. do not provide information on cytotoxicity in mammalian cells. Indeed, sources of information i. to iii. provide information concerning bacterial cells and not mammalian cells while source of information iv. does not provide any information on cytotoxicity. Therefore sources of information i. to iv. cannot contribute to the conclusion on cytotoxicity in mammalian cells.

Sources of information v. to ix. may provide relevant information on cytotoxicity in mammalian cells.

2) Frequency of gene mutations (mutant frequency)

Sources of information i. to v., vii. and viii. do not provide information on mutant frequency and therefore cannot contribute to the conclusion of this mandatory key investigation. In addition we note that the *in vivo* assays vii. and viii. provide only an indication of induced damage to DNA but do not provide direct evidence of mutation.

As for source of information ix. it may provide some relevant information on the frequency of gene mutations.

Based on the above, sources of information v., vii. and viii. provide information on cytotoxicity in mammalian cells however they do not provide information on gene mutations. Only sources of information vi. and ix. provide some information on cytotoxicity in mammalian cells and gene mutation in the same study.

However, as regards ix. the reliability of this source of information is significantly affected by the following deficiency:

- you have not established that relevant properties of the Substance can be predicted from data on the analogue substance, as explained in section 1.1 of the Appendix on Reasons common to several requests.

As for source of information vi. you do not report data on the cytotoxicity and the mutation frequency for the treated and control cultures, as required by OECD TG 476/490.

Therefore, based on the sources of information provided in your dossier and in your comments on the draft decision, even when considered together, it is not possible to conclude whether your Substance has or has not the particular dangerous property foreseen to be investigated in an OECD TG 476 or 490 study. Therefore, your adaptation is rejected.

B. Column 2 adaptation

Under Section 8.4.2., Column 2, second indent, Annex VIII to REACH, the study may be omitted if the Substance is known to be carc. 1A/1B or muta 1A/1B/2.

You have classified the Substance as Carc. 1B. However you refer to the hazard statement *"H341: Suspected of causing genetic defects' which comprises heritable genetic damage as well as somatic cell mutagenicity"*, which corresponds to Muta. 2 (H341) according to the CLP Regulation.

The Substance is not known to be carc. 1A/1B or muta 1A/1B/2. Therefore, the requirements of Section 8.4.2., Column 2, second indent, Annex VIII to REACH are not met.

Based on the above, the information requirement is not fulfilled.

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 using the thymidine kinase gene (OECD TG 490) are considered suitable.

2. Screening for reproductive/developmental toxicity

A Screening for reproductive/developmental toxicity study (test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) is an information requirement under Annex VIII to REACH (Section 8.7.3.), 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 an adaptation under Annex XI, Section 1.2. of REACH (weight of evidence) with the following supporting information on the Substance:

(i.) Combined repeated dose & carcinogenicity study in rats, oral route ([redacted], 2012)
(ii.) Combined repeated dose & carcinogenicity study in mice, oral route ([redacted], 2012)

You also provided the following information:

(iii.) QSAR prediction for NOEL value for 90 days based on read-across from selected analogue substances ([redacted], 2014)

Additionally, in your comments to the draft decision you also provided the following studies:

(iv.) Reproductive and developmental toxicity study, comparable to OECD TG 422, with the analogue substance 3-methylaniline (EC no. 203-583-1)
(v.) Reproductive and developmental toxicity study according to OECD 42, with the analogue substance 1-tert-Butyl-4-methylbenzene (EC no. 202-675-9).

In your comments to the draft decision you conclude that based on the sources of information (i.) to (v.) the Substance has "*the potential to adversely affect fertility, sexual function and offspring development*". Therefore you regard the Substance to be classified as "*H361: suspected of damaging fertility or the unborn child*". We understand with this comment that you are invoking an adaptation under Column 2 of Section 8.7.3, Annex VIII to REACH.

A. *Weight of evidence adaptation*

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

As explained in the Appendix on Reasons common to several requests we assessed this information and identified the following issues:

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 sources of information (i.) and (ii.) provide information on oestrous cyclicity and sperm parameters. However, they do not inform on mating, gestation (length), maintenance of pregnancy (abortions, total resorptions), parturition, lactation, litter sizes, nursing performance and other potential aspects of sexual function and fertility as forseen to be investigated in EU B.63/OECD TG 421 or EU B.64/OECD TG 422. Therefore, these 2 studies only provide limited information on sexual function and fertility.

Source of information (iii.) does not provide any information on sexual function and fertility. Therefore, this source of information cannot contribute to the conclusion on sexual function and fertility.

Sources of information (iv.) and (v.) provide relevant information on sexual function and fertility. However, the reliability of these sources of information is significantly affected by the deficiency described in section 1.1 of the Appendix on Reasons common to several requests. As explained in that section, you have not established that relevant properties of the Substance can be predicted from data on the analogue substances.

2) *Toxicity to offspring*

Information on pre- and perinatal 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.

Sources of information (i.) to (iii.) do not provide data on toxicity to offspring. Therefore, they cannot contribute to the conclusion on toxicity to offspring.

Sources of information (iv.) and (v.) provide relevant information on toxicity to offspring. However, the reliability of these sources of information are significantly affected by the deficiencies described above.

3) Systemic toxicity

Information on systemic toxicity include clinical signs, survival, body weights, food consumption, haematology, clinical chemistry, organ weights and histopathology of non-reproductive organs and other potential aspects of systemic toxicity in the parental generation up to postnatal day 13.

Source of information (iii.) does not provide any information on systemic toxicity. Therefore, the study cannot contribute to the conclusion on systemic toxicity.

Sources of information (i.), (ii.), (iv.) and (v.) provide relevant information on systemic toxicity. However, the reliability of sources of information (iv.) and (v.) is significantly affected by the deficiencies described above.

Based on the above, As regards sources of information (iv.) and (v.), while they provide information on sexual function and fertility, toxicity to offspring and systemic toxicity they have significant issues affecting their reliability, as explained above. Accordingly, only one of the key elements (systemic toxicity) is covered by sources of information (i.) and (ii.). There is only limited information on sexual function and fertility and no information available on toxicity to offspring.

Taken together, sources of information (i.) and (ii.), as indicated above, provide information on reproductive toxicity but essential parts of information of the hazardous property is lacking, including information on: mating, gestation (length), maintenance of pregnancy (abortions, total resorptions), parturition, lactation, litter sizes, nursing performance and other potential aspects of sexual function and fertility; and toxicity to offspring.

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

B. Column 2 adaptation

According to Annex VIII, Section 8.7., Column 2, third paragraph, the study does not need to be conducted if the substance meets the criteria for classification as toxic for reproduction category 1A or 1B: "May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment [...]". However, testing for effects on fertility must be considered.

You have self-classified the Substance as *"H361: suspected of damaging fertility or the unborn child"*, corresponding to Repr. 2 (H361D) according to the CLP Regulation.

Therefore your Substance is not known to be toxic for reproduction category 1A/1B. Therefore, the requirements of Section 8.7., Column 2, third paragraph, Annex VIII to REACH are not met.

Based on the above, the information requirement is not fulfilled.

Study design

A study according to the test method EU B.63/OECD TG 421 or EU B.64/OECD TG 422 must be performed in rats with oral[6] administration of the Substance.

2. 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.).

You have provided an adaptation under Annex XI, Section 1.2. of REACH (weight of evidence) with the following supporting information on the Substance:

(i) Acute toxicity to *Pimephales promelas* (guideline ASTM, 1980), S Broderius and M Kahl, 1985.
(ii) Acute toxicity to *Oryzias latipes* (guideline Japanese Industrial Standards Committee, 1971), Y Tonogai *et al*, 1982.
(iii) Acute toxicity to fathead minnow (guideline not specified), DL Geiger *et al*, 1986.

Based on the presented sources of information, you argue that the available data gives sufficient information to conclude on short-term toxicity on fish and you state: *'By applying weight of evidence approach to the studies above it can be observed that the LC50 values was found to be in range of 46 to 52 mg/l in 96 hrs and the EC50 values was found to be in the range of 41.5 to 52 mg/l in 96 hrs. Also the Median Tolerence limit (TLm) value was found to be in the range of 20 to 44 mg/l in 24 hrs study".*

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

To fulfil the information requirement, normally a study performed according to 203 must be provided. OECD TG 203 requires to investigate the following key investigation: the concentration leading to 50% mortality of the juvenile fish at the end of the test.

The sources of information (i), (ii) and (iii) provide relevant information on the concentration leading to 50% mortality of the juvenile fish, but these have the following deficiency affecting their reliability:

A study summary must be provided covering sufficient information to make an independent assessment of the study, including a description of the study design and procedure and the test results.

However, the study summaries you provided do not cover this critical information. Therefore, it is not possible to make an independent assessment of the studies.

The issues affecting the reliability of the sources of information are so significant that it is not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous property foreseen to be investigated in an OECD 203 study. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

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 15 April 2020.

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

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

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

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)[11]

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.

[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] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316

OECD Guidance documents[12]
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.

[12] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix F: Addressees of this decision and the corresponding information requirements applicable to them

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.