Helsinki, 18 December 2017

Addressee: [redacted]

Decision number: CCH-D-2114382036-51-01/F
Substance name: 2-(dimethylamino)-2-[(4-methylphenyl)methyl]-1-[4-(morpholin-4-yl)phenyl]butan-1-one
EC number: 438-340-0
CAS number: 119344-86-4
Registration number: [redacted]
Submission number: [redacted]
Submission date: 03/11/2016
Registered tonnage band: 10-100

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. **Degradation: Phototransformation of chemicals in water – direct photolysis (Annex VIII, Section 9.2.; test method OECD 316), including the identification of (photo)-degradation pathways and the rates at which they occur and the identification of the major (photo)-degradation products.**

2. **Long-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1., column 2; test method: Daphnia magna reproduction test, EU C.20./OECD TG 211) with the registered substance;**

3. **Long-term toxicity testing on fish (Annex VIII, Section 9.1.3., column 2; test method: Fish, early-life stage (FELS) toxicity test, OECD TG 210) with the registered substance;**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH Regulation. To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **25 June 2019.** You also have to update the chemical safety report, where relevant.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its

notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] by Claudio Carlon, Head of Unit, Evaluation E2

[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.

ECHA
EUROPEAN CHEMICALS AGENCY

Appendix 1: Reasons

1. Degradation: Phototransformation of chemicals in water – direct photolysis (test method OECD 316), including the identification of the major degradation products (Annex VIII, Section 9.2.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 10 to 100 tonnes per year must contain, as a minimum, the information specified in Annexes VII to VIII to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Degradation" is a standard information requirement as laid down in Annex VIII, Section 9.2. of the REACH Regulation, stating that "*Further degradation testing shall be considered if the chemical safety assessment according to Annex I indicates the need to investigate further the degradation of the substance. The choice of the appropriate test(s) will depend on the results of the chemical safety assessment.*"

You have conducted a ready biodegradability test according to Annex VII, Section 9.2.1.1., which concluded that the registered substance is not readily biodegradable. Nevertheless, you indicate that photodegradation is a relevant degradation pathway. However, you have not provided any information on:

1) Which (photo-)degradation pathways are possible and the rates at which they occur; and
2) Which (photo-)degradation products are formed.

ECHA considers that further information on degradation, particularly on the photodegradation products, is necessary for the PBT assessment under Annex XIII of the REACH Regulation and to fully characterise the risk assessment. In fact, while you have conducted a PBT assessment of the registered substance, this needs to be done also for its degradation products, as laid down in the fifth introductory paragraph of Annex XIII to the REACH Regulation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance:
Phototransformation of Chemicals in Water – Direct Photolysis (test method OECD 316), including the identification of (photo-)degradation pathways and the rates at which they occur and the identification of the major (photo-)degradation products.

2. Long-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1., column 2)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 10 to 100 tonnes per year shall contain as a minimum the information specified in Annexes VII to VIII of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Short-term toxicity testing on invertebrates" is a standard information requirement as laid down in Annex VII, Section 9.1.1. of the REACH Regulation. Furthermore, pursuant to Annex VII, Section 9.1.1., column 2, the long-term aquatic toxicity study on invertebrates (Annex IX, Section 9.1.5.) shall be considered if the substance is poorly water soluble. Adequate information on this endpoint needs to be present in the technical dossier for the

registered substance to meet this information requirement. The choice of the appropriate test(s) will depend on the results of the chemical safety assessment.
ECHA considers that substances that are poorly soluble in water require a longer time to be significantly taken up by the test organisms and so steady state conditions are not likely to be reached within the duration of a short-term toxicity test. For this reason, short-term tests may not give a true measure of toxicity for such substances and toxicity may actually not even occur at the water solubility limit of the substance if the test duration is too short. For such substances long-term aquatic testing is required to accurately assess the risks to the aquatic environment.

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) poorly water soluble substances have a water solubility below 1 mg/L or below the detection limit of the analytical method of the test substance. ECHA notes that the registered substance has a reported dissociation constant of 6.22 and consequently its water solubility is pH-dependent. With increasing pH the water solubility decreases, as the non-dissociated species predominates. This is confirmed by the two provided water solubility studies (according to OECD 105, reliability 1), showing a water solubility of 2.8 mg/L at pH 6.1 (20°C) and a water solubility of 1.9 mg/L at pH 6.8 (20°C). You have indicated that both water solubility studies were undertaken taking into account the light sensitivity of the registered substance.
In the technical dossier, you provided studies on the short-term toxicity to fish and aquatic invertebrates and a study with algae, showing no effects at the limit of water solubility (loading rate of 100 mg/L using a WAF approach). Analytical monitoring was provided in all studies showing mean measured concentrations of 0.17 mg/L in the short-term toxicity study to fish, below the limit of detection of 0.0643 mg/L in the short-term toxicity study to aquatic invertebrates and 0.09 mg/L in the study with algae. The short-term toxicity studies to fish and aquatic invertebrates were conducted at pH 7.9 in accordance with guideline recommendations (guideline recommends pH 7-8). You have indicated that the short-term toxicity studies to fish and aquatic invertebrates were undertaken taking into account the light sensitivity of the registered substance. ECHA notes that the measured concentrations at the start of exposure in these tests at pH 7.9 were significantly below the water solubility value of 1.9 mg/L (pH 6.8).

It is important to recognise that the maximum achievable dissolved concentration of a substance in the test medium, i.e. saturation concentration, may not be the same as the water solubility of the substance as determined by, for example, OECD Guideline 105. Typically, the concentration will be less. It is also important to note that water solubility measurements made for regulatory purposes are usually made in distilled water (pH= 6-9) whilst aquatic testing is carried out using various test media (pH=7-8). Differences in pH and chemical composition of the test media and distilled water may significantly affect the solubility, especially of ionised substances with a pKa between 5 and 9.
Based on the available information on dissociation and water solubility (from OECD 105 and short term aquatic toxicty tests) ECHA considers that the substance is poorly water soluble at envirionmentally relevant pHs above the dissociation constant (pKa). Hence, and as outlined above, short-term tests do not give a true estimation of the hazards observed for this substance as the duration of tests is not sufficient for effects to be observed (ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017).

For the reasons stated above, long-term toxicity needs to be investigated already at the tonnage band currently applicable for the substance subject to the present decision.

ECHA observes that no information on long-term toxicity to aquatic invertebrates is reported in the registration dossier. As already discussed above the short-term toxicity test on aquatic invertebrates provided in the technical dossier cannot be considered sufficient as the lack of toxicity at the short-term test cannot exclude long-term toxicity.

As outlined above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA notes that the present request was included in the decision following a Proposal for Amendment (PfA) submitted by a Member State Competent Authority (MSCA). In your comments on the PfA, you indicate that you wish to perform a new dissociation constant test, a refined hydrolysis test (concentrating in the pH range of pH 7 – 9) and the requested phototransformation test prior to conducting the aquatic long-term studies.

You indicate your concerns on the validity of the dissociation constant study submitted in the technical dossier, firstly due to there being no mention in the study report that the study was conducted under light exclusion conditions. ECHA acknowledges that in the Endpoint Study Record (ESR) submitted under IUCLID section 4.2.1. no reference is made to light exclusion conditions. Secondly, you indicate that the study may not be valid due to the OECD TG 112 guideline not being suitable for low water solubility substances. However, in the OECD TG 112 under "*test solutions*" it is indicated that solvents may be used to enhance solubility while in the ESR it is written that "*The addition of acetone was necessary due to the relatively low water solubility of test item. The acetone content should not influence the dissociation behaviour of test item*". Hence, ECHA notes that in the study conducted certain measures were taken in respect of the solubility issue. If you have additional information for this endpoint indicating that the current pKa value may not be accurate you should include this new information in the technical dossier and apply it in any relevant adaptation(s). ECHA will assess this dossier update in the follow up process. However, ECHA considers that the standard information requirement for the dissociation constant endpoint is currently fulfilled.

You also wish to study the hydrolysis of the substance at pH 7-9 to "*further investigate the the behaviour of the substance in water under different environmental conditions*". ECHA acknowledges your wish and considers that such investigation may provide further information on the behaviour of the substance in order to support the degradation and aquatic testing. However, ECHA considers that the standard information requirement for the hydrolysis endpoint is currently fulfilled.

You also consider that the current short-term toxicity tests evaluate the toxicity of the substance accurately, as Water Accomodated Fractions (WAFs) were used as described in the OECD 23 Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures. ECHA notes that according to the OECD 23 the WAFs approach may be used to assess the toxicity of complex multicomponent substances, "*The toxicity of complex multi-component substances, which are only partially soluble in water, can be determined by preparing water-accommodated fractions (WAFs) of them.*" ECHA notes that in your comments you refer to the substance as a monoconstituent. ECHA notes that based on the information in the technical dossier the registered substance is not a complex multi-constituent (it is a racemic mixture of isomers). Therefore, a WAF approach may not be the most appropriate approach. Also, ECHA considers that it is not possible to fully assess the toxicity of a low water solubility substance even if using the WAF approach for sample preparation due to the issues such as the time taken for the effects to be observed for a low

water solubilty substance described in ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) and as outlined above in this decision. In additon, ECHA also considers that the solubility being pH dependent, needs to be considered as this will affect the behaviour of the substance in water. ECHA also notes that you have indicated that in the short-term aquatic studies on invertebrates and fish the light sensitivity of the substance was accounted for. Consequently potential photodegradation alone cannot account for the test substance concentrations in the test media.

ECHA ackowledges that you may investigate the physciochemical properties of the substance further. However, based on the current information in the technical dossier, the need to study the long-term aquatic toxicity of the registered substance is evident due to poor water solubility of the substance at environmentally relevant pHs above the dissociation constant (pKa). ECHA considers that based on the information available the current dissociatio constant study is reliable and that the pKa of the substance falls in between of 5 to 9 and for such substances change in solubility is an issue as defined in ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017).

According to ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) *Daphnia magna* reproduction test (test method EU C.20. / OECD TG 211) is the preferred test to cover the standard information requirement of Annex IX, Section 9.1.5. The pH of the test medium should be above pH 7, as the non-dissociated form is regarded to be more toxic (OECD No. 21, 2006).

For dissociating nitrogen containing substances such as the registered substance there should be careful consideration of the pH to be used in the test as solubility may be lower but toxicity may be higher when the non-dissociated neutral form of the substance predominates at pHs above the dissociation constant (pKa). Furthermore, ECHA *Guidance on information requirements and chemical safety assessment, Chapter R.7b* (version 4.0, June 2017) indicates that the dissociated and non-dissociated species may have different water solubility and partition coefficient values, and therefore have different bioavailability and toxicity values.´

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Daphnia magna reproduction test (test method: EU C.20./OECD TG 211).

3. Long-term toxicity testing on fish (Annex VIII, Section 9.1.3., column 2)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 10 to 100 tonnes per year shall contain as a minimum the information specified in Annexes VII to VIII of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

"Short-term toxicity testing on fish" is a standard information requirement as laid down in Annex VIII, Section 9.1.3. of the REACH Regulation. Furthermore, pursuant to Annex VIII, Section 9.1.3., column 2, the long-term aquatic toxicity study on invertebrates (Annex IX, Section 9.1.6.) shall be considered if the substance is poorly water soluble. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement. The choice of the appropriate test(s) will depend on the results of the chemical safety assessment.

As fully explained above in request 2 ECHA considers that long-term toxicity needs to be investigated at the tonnage band currently applicable for the substance subject to the present decision.

ECHA observes that no information on long-term toxicity to fish is reported in the registration dossier. As already discussed above in request 2, the short-term toxicity test on fish provided in the technical dossier cannot be considered sufficient as the lack of toxicity at the short-term test cannot exclude long-term toxicity.

Therefore, for the reasons explained above in request 2, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information on long-term toxicity to fish for this endpoint.

ECHA notes also that the aquatic integrated testing strategy (ITS) given in *ECHA Guidance on information requirements and chemical safety assessment*, Chapter R.7b (version 4.0, June 2017), Section R.7.8.5.3.), is not applicable due to the following.

ECHA notes that for the derivation of the $PNEC_{aquatic}$ data on three trophic levels, on aquatic invertebrates, fish and aquatic plants, are required (ECHA Guidance on information requirements and chemical safety assessment, v.4.0, June 2017, Chapter R7b, Section R.7.8.5.3). As fully discussed in request 2, above, short-term toxicity tests are not reliable for this substance and consequently long-term data on all three trophic levels is needed for the derivation of $PNEC_{aquatic}$ and to perform the chemical safety assessment.

ECHA notes that the present request was included in the decision following a Proposal for Amendment (PfA) submitted by a Member State Competent Authority (MSCA). In request 2 above, ECHA has addressed your comments submitted on the PfAs. In summary, ECHA considers that long-term aquatic toxicity testing is required to fully assess the aquatic toxicity potential of the registered substance.

Regarding the test method, ECHA considers that the FELS toxicity test according to OECD TG 210 is the most sensitive of the standard fish tests available as it covers several life stages of the fish from the newly fertilised egg, through hatch to early stages of growth and should therefore be used (see ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Figure R.7.8-4). The test method OECD TG 210 is also the only suitable test currently available for examining the potential toxic effects of bioaccumulation (ECHA Guidance Chapter R7b, version 4.0, June 2017). For these reasons, ECHA considers the FELS toxicity test using the test method OECD TG 210 as appropriate and suitable. The pH of the test medium should be above pH 7, as the non-dissociated form is regarded to be more toxic (OECD No. 21, 2006).

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Fish, early-life stage (FELS) toxicity test (test method: OECD TG 210).

Notes for your consideration for requests 2 and 3 above

Once results of the test on long-term toxicity to invertebrates and to fish are available, you shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation.

Before conducting the above test you are advised to consult the ECHA Guidance on information requirements and chemical safety assessment, Chapters R.4 (v.1.1, December 2011), R.5 (v.2.1, December 2011), R.6 (May 2008), R.7b (v 4.0, June 2017) and R.7c (v 3.0, June 2017). If you decide to adapt the testing requested according to the specific rules outlined in Annexes VI to X and/or according to general rules contained in Annex XI of the REACH Regulation, you are referred to the advice provided in practical guides on "How to use alternatives to animal testing to fulfil your information requirements for REACH registration".

Due to the physicochemical and/or degradation properties of the registered substance, you should consult OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures, ENV/JM/MONO (2000)6 and ECHA *Guidance on information requirements and chemical safety assessment* (version 4.0, June 2017), Chapter R7b, Table R.7.8-3 summarising aquatic toxicity testing of difficult substances for choosing the design of the requested ecotoxicity test(s) and for calculation and expression of the result of the test(s).

Deadline to submit the requested information in this decision

In the draft decision communicated to you the time indicated to provide the requested information was 6 months from the date of adoption of the decision. Following Proposals for Amendment (PfAs) submitted by a Member state competent Authority, requests 2. and 3. were included to the draft decision. Also, taking into account the registrants comments on the PfAs, concerning the registered substance being difficult to test the deadline set for the decision has been modified. ECHA has granted a deadline of 18 months from the date of adoption of the decision.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 24 October 2016.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, 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.

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

In addition, you provided comments on the draft decision. These comments were not taken into account by the Member State Committee as they were considered to be outside of the scope of Article 51(5).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-57 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.