

Committee for Risk Assessment
RAC

Annex 2
Response to comments document (RCOM)
to the Opinion proposing harmonised classification and
labelling at EU level of

**2-benzyl-2-dimethylamino-4'-
morpholinobutyrophenone**

EC Number: 404-360-3
CAS Number: 119313-12-1

CLH-O-0000001412-86-145/F

Adopted
15 March 2017

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 2-BENZYL-2-DIMETHYLAMINO-4-MORPHOLINOBUTYROPHENONE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: 2-benzyl-2-dimethylamino-4-morpholinobutyrophenone

EC number: 404-360-3

CAS number: 119313-12-1

Dossier submitter: Germany

GENERAL COMMENTS

| Date | Country | Organisation | Type of Organisation | Comment number |
|--|---------|--------------|----------------------|----------------|
| 21.07.2016 | France | | MemberState | 1 |
| Comment received | | | | |
| FR MSCA does not support the proposal of declassification of 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone (CAS: 119313-12-1) as Aquatic Acute 1, H400 and Aquatic Chronic 1, H410. Clarifications and additional information are needed in order to re-evaluate the dossier concerning environmental hazards. | | | | |
| Dossier Submitter's Response | | | | |
| Thank you for your comment. Please consider the response to comment number 3. | | | | |
| RAC's response | | | | |
| RAC agrees and welcomes the new information presented. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---------|-------------------------------|------------------------|----------------|
| 15.06.2016 | Germany | GEELIO Umwelttechnologie GmbH | BehalfOfAnOrganisation | 2 |
| Comment received | | | | |
| We agree with the classification proposal for Environment from BAuA Germany: No classification for Environment. | | | | |
| Dossier Submitter's Response | | | | |
| Thank you for your comment. | | | | |
| RAC's response | | | | |
| RAC is of the opinion that there is not enough data to declassify. Please see the RAC Opinion. | | | | |

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OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

| Date | Country | Organisation | Type of Organisation | Comment number |
|--|---------|--------------|----------------------|----------------|
| 21.07.2016 | France | | MemberState | 3 |
| Comment received | | | | |
| <p>FR MSCA does not support the proposal of declassification of 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone (CAS: 119313-12-1) as Aquatic Acute 1, H400 and Aquatic Chronic 1, H410. The information presented in the classification dossier does not allow declassifying the substances in the actual entry in annex VI. Clarifications and more information are needed in order to re-evaluate the dossier concerning environmental hazards.</p> <p>1. Page 12 and 15. According to data presented in the classification dossier, the substance exhibits a water solubility of 5.9 mg/L, a log Pow of 2.91 and it is considered as not ready biodegradable. However, some inconsistencies are detected in the dossier concerning water solubility. In page 15, section 5.4.1.1 Short-term toxicity to fish, the loading rate nominal of 10 mg/L was chosen with regard to the expected water solubility of 0.75 mg/L (buffer solution pH 7) and 0.03 mg/L (buffer solution pH9), these values are not consistent with the water solubility reported of 5.9 mg/L. Please clarify this point.</p> <p>2. Considering the water solubility of 5.9 mg/L and the measured concentrations of the substances in the ecotoxicity tests (acute fish test, daphnia long term test and algae test), it is not possible to state that no effects occurred within the range of solubility because highest concentrations were not tested. Justifications about the choice of nominal loading rate tested and more information about conditions of ecotoxicity test performed are needed to clarify this point.</p> <p>3. Table 19 (page 21), it would be better if the summary of data is presented in nominal loading rate and measured concentrations.</p> | | | | |
| Dossier Submitter's Response | | | | |
| <p>1.+2.) We agree with you, that the water solubility values from the ecotoxicity studies are not consistent with the one derived from the water solubility test. The discrepancy is not explainable for us. But the measurements and observations in the algae toxicity test fit to the measurements of the fish short-term toxicity study conducted by Dr. U.Noack-Laboratorien. There, during the first 24 hours the concentrations decreased to 0.1 mg/L (initially measured: 0.18 mg/L) and below 0.5 mg/L (initially measured: 1.0 mg/L) and the test concentrations stabilized at ca. 0.1 mg/L during the remaining part of the test period.</p> <p>The Limit-concentration in the study (DR. U. NOACK-LABORATORIEN 2014) was prepared by mixing the test substance with dilution water and stirring for 24 hours with a magnetic stirrer at room temperature without light. Afterwards the undissolved particles were removed by using a membrane filter (0.45 µm). The test concentration was measured with LC-MS/MS: new media at 0h: 0.216 mg/L, old media at 24h: 0.0776 mg/L, new media at 72h: 0.190 mg/L and old media at 96h: 0.127 mg/L. The geometric mean of the measured concentrations was 0.142 mg/L. The loading rate was 0.84 g fish per litre test solution. The mean length at the start of the experiment was 27 mm. The average weight was 0.24 g. 7 fishes were used per concentration and control. The glass aquaria contained 2 litres (volume: 3L) and were covered with glass plates. In the preliminary test (3 fish) no effects (lethal or sublethal) were observed. The measured concentration was at test beginning 0.449 mg/L and after 24h 0.207 mg/L. The pH values in the definitive test were 6.89 to 7.67.</p> | | | | |

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In the older test (Ciba AG 1988) a solvent was used. The preparation of the test solutions was the following: 3 g test substance and 80 mg alkylphenol-polyglykol-ether mixed and made up to 25 mL with 1-methyl-2-pyrrolidon (NMP). The highest vehicle concentration was 245 mg/L. Nominal concentrations were: 1.8 – 3.2 – 5-8 – 10 – 18 – 32 mg/L. And the measured concentrations were: 0.1 – 0.2 – 0.1 – 0.3 – 0.5 – 0.6 mg/L. A control and solvent control were used. No effects occurred in the controls. Small parts of the test substance were swimming at the surface of all concentrations from the start of the test. A slight deposit was observed after 24h exposure at conc. 3.2-32 mg/l nominal. The loading rate was 0.09 g fish per litre test solution. The mean length at the start of the experiment was 26 mm. The average weight was 0.14 g. 10 fish were used per concentration and control. The glass aquaria contained 15 litres (volume: 20L). The pH values were 8.0 to 8.4. There was no (lethal or sublethal) effect at nominal 10 mg/L and measured 0.3 mg/L. At the two highest test concentrations (measured: 0.5 and 0.6 mg/L) 9 and 7 fish died. The other fish in the two highest test concentrations showed severe loss of balance and also moderate effects on the swimming behavior. At 0.3 mg/L (real) and lower concentrations no effects on fish occurred. The test was considered as not reliable as very high amounts of emulsifier were used and small parts of the test substance were swimming at the surface of the test concentrations.

In our opinion the preparation method of the newer short-term fish toxicity test seems well-suited for the dilution of the maximum soluble amount of the test substance.

3.) Thank you for this comment. We agree with you.

| Criteria for environmental hazards | 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone | Conclusion |
|---|--|--|
| <p>Acute toxicity data: LC₅₀/EC₅₀/ErC₅₀ ≤ 100 mg/L</p> <p>Chronic toxicity data: NOEC ≤ 1 mg/L</p> | <p>Fish: LC₅₀ > 10 mg/L (loading rate, no acute effects within the range of solubility in the test medium) LC₅₀ > 0.142 mg/L (real, mean measured)</p> <p>Invertebrates: NOEC 21 d ≥ 10 mg/L (loading rate) NOEC 21 d ≥ 0.21 mg/L (real, mean measured; no chronic effects within the range of solubility in the test medium)</p> <p>Algae: ErC₅₀ 72 h > 100 mg/L (loading rate) ErC₅₀ 72 h > 2 mg/L (real, initial; no effects within the range of solubility in the test medium)</p> <p>Water solubility (in distilled water) = 5.9 mg/L</p> | <p>No acute and chronic toxicity within the range of solubility</p> |

RAC's response

1.+2. RAC refers to the OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures (OECD Series on Testing and Assessment N°23) where it is stated in Chapter 3.2:

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"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) and not test media (pH=7-8) and that differences in pH of the test media and distilled water may significantly affect the solubility, especially of ionised substances with a pKa between 5 and 9. If it is necessary to assess the toxicity of a substance at the saturation concentration, it is important to provide evidence that all reasonable efforts have been taken to achieve this. An effect concentration can be measured only if it is equal to, or less than, the saturation concentration. If an effect cannot be detected in a test with a saturated solution the result should be reported as no toxic effects at saturation. It is important to note that an absence of acute toxic effects at the saturation concentration cannot be used as the basis for predicting no chronic toxicity at saturation or at lower concentrations." Please see the RAC Opinion for more details.

| Date | Country | Organisation | Type of Organisation | Comment number |
|------------|---------|--------------|----------------------|----------------|
| 19.07.2016 | Belgium | | MemberState | 4 |

Comment received

Notwithstanding the fact that there are several REACH registration dossiers available for 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone, we regret that only water solubility and partition coefficient are reported as physicochemical properties. Also other properties like vapour pressure, Henry's law constant, dissociation constant, surface activity,... can help in the interpretation/evaluation of aquatic toxicity data.

Data from these registration dossiers show for this substance a surface tension of 59.1 mM/m indicating that 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone is surface active. Dissociation constant : Pka1 =6.3 and pKa2=1.6 at 25°C.

Furthermore it is difficult to decide on the proposal to delete environmental classification based on the information given in the CLH report and to decide on the reliability or not of the available studies.

In some studies a saturated solution was used for aquatic toxicity testing due to a low water solubility and the photolysis of the substance, however

- No data on photodegradation are provided in the CLH report
- Water solubility value is only reported for the short term toxicity study in fish (0.75 mg/l-pH7 and 0.03mg/l-pH9)
- pH range in the different studies?
- a saturated test solution of 10 mg/l test substance was used for fish and invertebrates, except for algae were 100 and 200 mg/L test substance was used.
- results of the preliminary experiment should be reported more in detail (techniques used) as they form a reference point (i.e. water solubility under test conditions) against which the test results can be evaluated
- ...

Despite that emulsifier was used in excess of the highest recommend value of OECD TG (> 100mg/l), what is the effect of the emulsifier in these studies? What were the tested concentrations of the substance in these studies? When precipitation/floating particles were observed, was exposure concentration measured? Did these particles lead to

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|---|----------------|---------------------|-----------------------------|-----------------------|
| physical effects? | | | | |
| Dossier Submitter's Response | | | | |
| No information on photodegradation are available in the registration dossiers. | | | | |
| <p>Concerning the short-term fish toxicity study (Ciba AG 1988) emulsifier was used in excess of the highest recommended value of OECD TG and small parts of the test substance were swimming at the surface of all concentrations from the start of the test. A slight deposit was observed after 24 h exposure at concentrations above 0.1 mg/L (measured). The observed fish were not affected up to a concentration of 0.3 mg/L (measured) and then 9 and 7 of 10 fish died. The other 1 and 3 fish in the two highest test concentrations showed severe loss of balance and also moderate effects on the swimming behavior. It is possible that this was due to the higher amount of small parts swimming on the surface of the test solution but also because the amount of emulsifier was highest in the highest test concentrations.</p> <p>In the algae toxicity studie a rapid decrease of the concentrations in the test solution was observed within the first 24 hours (from 2.0 mg/L initial to below 0.5 mg/L at 24 h). So saturated test solutions of 100 and 200 mg/L were used but concentrations of 0.18 and 1.0 mg/L were measured initially. During the first 24 hours the concentrations decreased to 0.1 mg/L and below 0.5 mg/L. The test concentrations stabilized at ca. 0.1 mg/L during the remaining part of the test period. These observations fit to the measurements in the fish short-term toxicity study conducted 2014 by Dr. U. Noack-Laboratorien.</p> <p>The pH ranges in the other studies were: Daphnia long-term toxicity study: 7.7 to 7.9 Algae toxicity study: 8.0 to 8.1 Older fish short-term toxicity study: 8.0 to 8.4 Newer fish short-term toxicity study: 6.89 to 7.67</p> | | | | |
| RAC's response | | | | |
| <p>1. RAC agrees.</p> <p>2. RAC agrees that dissociation constants are very important and should have been included in the CLH Report. The surface tension in the REACH Registration dossier was determined to be 59 - 65 mN/m at 20°C (Filtrates of 10.0 g/L suspensions). RAC notes also that in Council Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to REACH it is stated that "considering that distilled water has a surface tension of 72.75 mN/m at 20 °C, substances showing a surface tension lower than 60 mN/m under the conditions of this method should be regarded as being surface-active materials". This issue has not been discussed in the CLH Report.</p> | | | | |
| Date | Country | Organisation | Type of Organisation | Comment number |
| 01.07.2016 | Finland | | MemberState | 5 |
| Comment received | | | | |
| <p>The FI CA does not support the removal of Aquatic Acute 1 H400 - Very toxic to aquatic life and Aquatic Chronic 1 H410 - Very toxic to aquatic life with long lasting effects classifications for 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone.</p> <p>There is not enough data in the CLH proposal to assess the reliability of the new studies which the removal of environmental classification is based on. In order to do so the study conditions should be described more in detail. In addition, the justification why Water</p> | | | | |

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| Soluble Fraction –method suitable for complex substances has been used for 2-benzyl-2-domethylamino-4'-morpholinobutyrophenone, is needed. Data on photolysis is missing even though it is mentioned in the study descriptions that the substance is photosensitive. It could also be useful to compare how this property has been taken into account in the previous studies. |
| Dossier Submitter's Response |
| No information on photodegradation are available in the registration dossiers. Please see responses to comment number 3 and 4. |
| RAC's response |
| RAC agrees to the FIN CA comments. More data have been found from the REACH registration dossier but still information on e.g. photolysis is missing. Please see the RAC opinion. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|------------|----------------|--------------|----------------------|----------------|
| 18.07.2016 | United Kingdom | | MemberState | 6 |

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| Comment received |
| <p>The proposal for the removal of the environmental classification hinges on the validity of the Ciba 1988 acute toxicity to fish study. We consider further information is required to consider the study not reliable.</p> <p>From the CLH report, the following details are unclear:</p> <ul style="list-style-type: none"> - was a solvent control included for comparison with exposure treatments? - what was the concentration of emulsifier for each exposure concentration? (we note the use of emulsifiers were within the scope of the test guidelines at the time (OECD 203, 1984)). - what impact could the presence of emulsifier >100mg/l have had, if any? - what impact could the presence of particulate have had, if any? - why is the measured concentration of 0.46 mg/l considered above the water solubility? - as the study pH was within the test guideline range, what additional non-substance related effects may have occurred? - was a clear dose-response observed? <p>In addition, it would be useful for the authors to present further information such as QSAR predictions or read-across for structural analogues to support the proposed position of no acute effects in fish up to the limit of solubility.</p> |

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| Dossier Submitter's Response |
| <p>Please see also the response to comment number 4.</p> <p>A solvent control was included and no effects were observed. The concentration of emulsifier for each exposure concentration is not reported in the study report. Small parts of the test substance were swimming at the surface of all concentrations from the start of the test. A slight deposit was observed after 24h exposure at concentrations above 0.1 mg/L (measured). This together with the observations in the algae toxicity test [During the first 24 hours the concentrations decreased to 0.1 mg/L (initially measured: 0.18 mg/L) and below 0.5 mg/L (initially measured: 1.0 mg/L) and the test concentrations stabilized at ca. 0.1 mg/L</p> |

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during the remaining part of the test period] it seems plausible that the maximum achievable solution of the test substance is in the range of 0.1 mg/L in test medium. Concerning the pH range in the older fish short-term toxicity study 8.0 to 8.4 are at the upper region of the pH range accepted in the OECD guideline and therefore it is possible that there is already an influence on the fish. Additionally, as the test substance has a lower solubility in more basic pH ranges this could also have had an impact, as well as the small parts swimming at the water surface (maybe the more the higher the concentrations was – this was not described in detail). In the study (Ciba AG 1988) there was no clear dose-response curve as up to the measured concentrations of 0.3 mg/L no effects were observed. At the two highest test concentrations (measured: 0.5 and 0.6 mg/L) 9 and 7 of 10 fish died. The other 1 and 3 fish in the two highest test concentrations showed severe loss of balance and also moderate effects on the swimming behavior.

RAC's response

RAC has used information given by the DS in this document and information from the REACH registration dossier. Please find more details in the RAC Opinion.