Committee for Risk Assessment

RAC

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

15 March 2017

CLH-O-0000001412-86-145/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone**

EC Number: **404-360-3**

CAS Number: **119313-12-1**

The proposal was submitted by **Germany** and received by RAC on **19 May 2016.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **7 June 2016**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **22 July 2016**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Riitta Leinonen**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **15 March 2017** by **consensus**.

Existing Annex VI entry (CLP, Table 3.1)

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	606-047-00-9	2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone	404-360-3	119313-12-1	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410	-	-	-
Dossier submitters proposal	606-047-00-9	2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone	404-360-3	119313-12-1	**Remove** Aquatic Acute 1 Aquatic Chronic 1	**Remove** H400 H410	**Remove** GHS09 Wng	**Remove** H410	-	-	-
RAC opinion	606-047-00-9	2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone	404-360-3	119313-12-1	**Retain** Aquatic Acute 1 Aquatic Chronic 1	**Retain** H400 H410	**Retain** GHS09 Wng	**Retain** H410			
Resulting Annex VI entry if agreed by COM	606-047-00-9	2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone	404-360-3	119313-12-1	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410	-	-	-

GROUNDS FOR ADOPTION OF THE OPINION

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

2-Benzyl-dimethylamino-4'-morpholinobutyrophenone (BDMBP) is used as a photosensitive agent in printing inks, pigmented coatings and photopolymers for imaging applications. It is a racemic mixture with a purity range between 98 and 99.9%. The dissociation constant of the test substance was calculated to be pKa1= 6.3 (basic, aliphatic tertiary amine) and pKa2= 1.6 (basic, aromatic tertiary amine in Morpholino ring) at 25°C. The current classification is Aquatic Acute 1 , H400 and Aquatic Chronic 1, H410 in Annex VI of the CLP Regulation. The Dossier Submitter (DS) proposed to remove the current classification due to data from new studies which do not have similar defiencies to the old studies that had been used to derive the current classification.

Degradation

Hydrolysis was studied according to EEC Dir. 84/449 C.10. The test substance was stable at pH 4 and pH 7. However, the hydrolysis test could not be performed at pH 9 because the solubility of the test substance in the buffer solution was too low. It is mentioned in the REACH registration dossier that the solutions of the test substance are very sensitive to light. Therefore, the solutions were prepared and handled under red light and stored in the dark.

There was no data on photodegradation. However, it is mentioned in relation to e.g. aquatic studies that the test substance solutions are sensitive to light.

In the ready biodegradability test conducted according to GLP and OECD 301B, 0% and 3% biodegradation was observed after 28 days with 10 and 20 mg/L of test substance, respectively. Consequently, the substance cannot be considered as readily biodegradable. There was no data on light conditions but according to the guideline the test is to be done in dark or diffuse light.

No other degradation tests were available.

Bioaccumulation

No reliable bioaccumulation study is available. There is a Japanese 8 week study with a one page study summary in English in the REACH registration dossier giving fish BCF values 133.1-278.6 and 120.8-298 at concentrations 0.2 ppm and 0.02 ppm, respectively. The details of the test conditions are, however, lacking. The log Pow reported in the CLH Dossier is 2.91 which would indicate that the potential for bioaccumulation is low for 2-benzyl-2-dimethylamino-4'morpholinobutyrophenone. It can be seen in the REACH registration dossier that the log Pow was determined according to OECD 107, at pH 6.1 and 25°C. In the first extraction experiment, some test substance and an unknown amount of impurities were eliminated.Consequently these substances are missing in the mass balance based on the actual weight. There is no data available on the light conditions.

Aquatic toxicity

The water solubility of BDMBP is 5.9 mg/L in distilled water at pH 6.8 and 20°C.

Short-term toxicity

There were two studies on fish, one study on *Daphnia magna* and two studies on algae available to assess short-term aquatic toxicity.

Table: Short-term toxicity to aquatic organisms

Method	Test species	Test duration and light conditions	Effect parameter	Effect (mg/L)
Modified OECD 203 (2014), GLP, freshwater, semistatic(daily renewal of Water Soluble Fraction), limit test	*Danio rerio*	96 h dark, pH6.0-8.5	LC50	>10 nominal (loading rate), no effects >0.142 measured (geometric mean), no effects
OECD 203 (1988), GLP, freshwater, static	*Brachydanio rerio* (new name *Danio rerio*)	96 h 16 h daily, fluorescent light, pH8.0-8.4	LC50	0.46 measured (96h) Emulsifier used in excess, small parts, deposit
OECD 202 (1988), GLP freshwater, static	*Daphnia magna*	24 h 16 h daily, fluorescent light ~ 2000 lux pH7.7-7.9	EC50 mobility	>100 nominal, no effects > 0.8 measured, no effects Emulsifier used in excess, small parts, deposit
OECD 201 (1996), GLP, freshwater, water accommodated fractions, static, limit test	*Selenastrum capricornutum* (new name: *Pseudokirchneriella subcapitata*)	72 h continuous 6500-8000 lux, pH8.0-8.4	E_rC50	> 100 (loading rate), no effects > 2 measured initial, no effects
ABC Protocol No. 9207 (1993), freshwater, static, screening study	*Scenedesmus subspicatus* (new name *Desmodesmus subspicatus*)	72h light conditions not known pH7.4	E_rC50	4 mg/L estimated acetone used as solvent

Both fish studies were conducted according to the OECD 203 Guideline. In the newer study (2014), the OECD 203 Guideline was modified to use Water Soluble Fraction (WSF) due to the low solubility of the test substance. The test was a semi-static limit test with daily renewal of the WSF. In the response to comments (RCOM), the DS explained that the limit concentration 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. The test concentration was measured: 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 loading rate of nominal 10 mg/L was chosen which clearly exceeds the reported solubility values, namely 0.75 mg/L in buffer solution pH7 and 0.03 mg/L in buffer solution pH9. The measured initial concentrations were within this range. Due to the light sensitivity of the test substance solutions, all preparation steps were carried out under red light. The stirring phase and the test were done in the dark. Samples for the determination of the test item analysis were handled under light exclusion. After 96 hours no effects occurred within the range of solubility. The 96 h LC50 was > 0.142 mg/L based on geometric mean of the measured concentrations.

The DS did not regard the older (1988) fish study as reliable since the test item was applied using a very high amount of an emulsifier (244 mg 1-methyl-2-pyrrolidone and 1 mg alkylphenol-polyglycol-ether per liter water in the concentration used for the highest concentration),

exceeding the maximum amount of 100 mg/L recommended in the OECD 203 Guideline. Due to the emulsifier, the test concentrations are higher than the water solubility. Additionally, deposits were observed after 24 h in all but the lowest test concentration. Moreover, the pH value of 8.0-8.4 is at the upper limit of recommended values and could lead to additional non-substance-related toxic effects. The photoperiod was, according to the REACH registration dossier, 16 hours daily in fluorescent light. The test concentration declined from 24-41% of the nominal at 0 h to 2-6 % of the nominal at 96 h. The 96 h LC50 was 0.46 mg/L based on measured concentrations. In a response to public consultation (PC) comments, the DS explained that a control and solvent control were used. No effects occurred in the controls.

A short-term toxicity study on Daphnia magna was conducted following GLP and OECD 202 Guideline. The DS considered the test not to be reliable since the test item was applied using an emulsifier (718 mg/L acetone and 3 mg/L alkylphenol-polyglycol-ether) for the highest concentration, exceeding the maximum amount recommended in the OECD 23 Guidance Document. Additionally, small amounts of undissolved material were floating at the surface of the test solution from the start of the test at 100 mg/L nominal and at 18-100 mg/L after 24 h exposure. The test duration was 24 h. According to the REACH registration dossier, the photoperiod was 16 hours daily and the light intensity was approximately 2000 lux, from a fluorescent light (REACH registration dossier).

In the algae study following GLP and OECD 201, saturated solutions with nominal concentrations of 100 and 200 mg/L were used due to the low solubility of the test item. Filtration was used. Test solutions were stored in the dark. Measured concentrations were at the most 2 mg/L. According to information found in REACH registration dossiers the photoperiod was continuous and light intensity and quality were 6500-8000 lux with the test substance being rapidly degraded by photolysis. No inhibition of algal growth was observed during a range-finding test at initial exposure concentrations ranging from 0.002 to 2.35 mg/L. In a subsequently performed limit test, significant inhibition of algal growth was recorded in the treated solutions (18-22%). The initial test concentrations were 1.5 and 2.0 mg/L. It was decided to repeat the tests because of relatively high variation between the extinction values of the different replicates, including those recorded in the control replicates. Concentrations measured at the start of a second limit test ranged from 0.18 to 1.0 mg/L. In the RCOM, the DS explained that during the first 24 hours the concentrations in the test decreased to 0.1 mg/L (initially measured 0.18 mg/L) and below 0.5 mg/L (initially measured 1.0 mg/L), respectively. The test concentration stabilized at ca. 0.1 mg/L during the remaining part of the test period. This time there was little variation between the extinction values of the untreated replicates and no inhibition of cell growth was recorded in any of the treated solutions. The EC50 values for both cell growth inhibition and growth rate reduction were greater than the maximum attainable concentration of approximately 2 mg/L.

The second algae study was conducted as a screening study not following any OECD guideline but conducted according to an internal protocol of the test facility. Acetone was used as solvent. There was no analytical monitoring of the test substance. Precipitation of the test substance was observed at 10 mg/L at the beginning of the test. After 72 h no precipitate was observed in any of the solutions. The DS considered this study not to be reliable due to its many deficiencies.

Long-term toxicity

There was one long-term aquatic toxicity study available for each of fish, Daphnia and algae, respectively.

Table: Long-term toxicity to aquatic organisms

Method	Test species	Test duration and light conditions	Effect parameter	Effect (mg/L)
OECD 210 (1996), GLP, freshwater, semi-static	*Brachydanio rerio* (new name *Danio rerio*)	29 d adjusted to 35-45 lux. pH7.8±2	NOEC	**Not valid** (survival of in the control group only 33.8%)
OECD 211 (2009), GLP, freshwater, semi-static, limit test	*Daphnia magna*	21d 16 h light, intensity 0.09-0.18 µE m^{-2} s^{-1}, pH7.6-7.8	NOEC reproduction, immobilisation, length of parental daphnids	> 10 (loading rate), no effects > 0.21 initial measured, no effects
ABC Protocol No. 9207 (1993), freshwater, static, screening study	*Scenedesmus subspicatus* (new name *Desmodesmus subspicatus*)	72h light conditions not known	NOErC	0.1 mg/L nominal acetone used as solvent

There is no reliable long-term toxicity study available for fish. In a semi-static GLP guideline study from 1996 following OECD 210, a saturated solution of 10 mg/L (nominal) was used due to the low solubility of the test substance. Additionally, due to the photosensitivity of the test item a semi-static exposure was chosen and the light intensity was adjusted from approximately 1000 lux to 35-45 lux. However, the study was discarded as during the transition from the yolk-sac phase to the phase of active feeding, survival rates rapidly decreased in almost all vessels. After 29 days the overall survival of the larvae in the control group was 33.8%, the acceptability criteria in the guideline being > 70% post hatch survival. Consequently, the validity criteria of the test was not fulfilled.

A semi-static study following GLP and OECD 211 was conducted on *Daphnia magna*. Due to the low solubility of the test item a saturated solution was used. According to the data in the REACH registration file, ultrasonication and intense stirring on a magnetic stirrer was used to dissolve a maximum amount of the test item. After that, the solution was filtered and used as the test solution. The test solutions were protected from daylight or UV-light. The photoperiod was 16 h light, 8 h dark. Light intensity was 0.09 to 0.18 µE m^{-2} s^{-1}. No effect on the test organisms were observed at 100% of the saturated solution at 10 mg/L. The mean measured concentration was determined to be 0.21 mg/L indicating that the NOEC is greater than 0.21 mg/L.

The algae study is not considered reliable as explained in relation to the short-term toxicity.

Comments received during public consultation

Four Member States and one industry (IND) organisation commented on the CLH Proposal during the Public Consultation (PC). Two Member States (MS) did not support the proposal to remove the classification of 2-benzyl-2-dimethylamino-4-morpholinobutyrophenone. All MSs requested clarifications and additional information. One MS pointed to the inconsistencies concerning the different water solubility values. The DS agreed that the water solubility values from the ecotoxicity studies are not consistent with the value derived from the water solubility test but could not explain why. They also gave more information on the short term fish toxicity key study. Another MS wanted more physicochemical properties presented in the CLH report in addition to the water solubility and partition coefficient. For example vapor pressure, the Henry's law constant, dissociation constant and surface activity could help interpretation of aquatic toxicity

data. The MS informed that information found in REACH registration dossiers includes the surface tention of 59.1 mM/m, which indicates that the substance is surface active[1], and has dissociation constants Pka1=6.3 and pKa2=1.6 at 25°C. The information given in the CLH Report was considered insufficient for evaluating the reliability of the studies. For example, the substance seems to be photosensitive but no information on photolysis is presented. One MS asked for a justification for the use of the WSF method for this substance. More information on the impact of the emulsifier used in excess and the particles in two studies was requested. The DS answered that no information on photodegradation was available and gave more information on the new key fish study and on the older fish study. More information on the concentrations in the key algae test was given.

One industry (IND) comment supported the proposal to declassify.

Assessment and comparison with the classification criteria

RAC is of the opinion that clarification of the light sensitivity of the substance in the CLH Report would generally have helped to evaluate the reliability of the aquatic tests.

Degradation

2-Benzyl-2-dimethylamino-4'-morpholinobutyrophenone does not hydrolyse at pH 4 and pH 7. The test could not be performed at pH 9 due to low solubility. There is no data on photolysis. The substance is not readily degradable (0% and 3% biodegradation after 28 days in OECD 301B). RAC agrees with the DS to consider the substance as not rapidly degradable.

Bioaccumulation

There is no reliable BCF data available. The log Kow of 2.91 (OECD 107) would indicate low potential for bioaccumulation. However, it is not clear if the result is affected by the light sensitivity of the substance. The substance is also surface active which may have an effect on the reliability of the test result.

Aquatic toxicity

There is a difference between water solubility of BDMBP in distilled water (5.9 mg/L) and in aquatic toxicity tests (> 0.1 mg/L). Such differences are quite common, as explained in the OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures. [2]

In two older acute tests on fish (*Danio rerio*) (1988) and *Daphnia* (1988), excess amounts of emulsifier were used at the highest dose. The reporting of the studies is not comprehensive. It is not known whether the level of emulsifier was too high in all treatments. In the solvent control, no effects were seen. Small amounts of undissolved material were floating at the surface and a

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[1] COUNCIL REGULATION (EC) No 440/2008 A.3. Surface tension: Considering that distilled water has a surface tension of 72,75 mN/m at 20 oC, substances showing a surface tension lower than 60 mN/m under the conditions of this method should be regarded as being surface-active materials.

[2] OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures (OECD Series on Testing and Assessment N°23) states that "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."

slight deposit was observed. RAC is of the opinion that in the older studies for acute toxicity some of the apparent toxicity measured may have been due to either achieving higher experimental concentrations than was achievable in the newer ones (e.g. due to pH or the loading method) or the toxicity of photodegradants which presumably were not present in those studies that used red light. Consequently, RAC does not agree with the DS to reject these tests altogether. Mortality was observed and there is no convincing evidence of a physical effect. QSAR calculations (See the Background Document) predict acute toxicity at or just below the water solubility.

There are also three reliable results from newer aquatic toxicity tests: LC50, 96 h, fish, >0.142 mg/L (measured), showing no effects and NOEC, 21 d, Daphnia, > 0.21 mg/L (measured), showing no effects. Poor solubility and light sensitivity has been taken into account in these tests. In addition, there is one reliable algae test showing no effects at ErC50 72 h, > 2 mg/L (measured), although it is performed under normal light conditions.

The DS's proposal to remove the aquatic classification is based on this data, acute toxicity information on fish and algae and chronic information on *Daphnia magna*. However, it is stated in the OECD Guidance Document 23 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. Consequently, the use of the surrogate system using the acute toxicity data in combination with degradability and/or bioaccumulation for chronic classification is not possible in this case. The lack of information regarding light sensitivity of the substance and possible reactions in the test media adds to the uncertainties.

Supporting information from additional key elements

The class-specific QSAR calculations for aliphatic amines predict acute LC/EC50 values for fish, Daphnid and green algae from 0.118 to 1.598 mg/L. The chronic ChV values for fish, Daphnid and green algae range from 0.028 to 0.048 mg/L.

Conclusions

The factors to be taken into account in a weight-of-evidence approach for BDMBP classification are:

- there is no reliable test data on chronic toxicity for algae and fish.
- the surrogate system used for the old fish data (1988) gives Aquatic Chronic 1 classification and for the newtest (2014) it cannot be used because of absence of acute toxic effects at the saturation concentration
- the old aquatic toxicity tests cannot be rejected
- the QSAR calculations show that acute toxicity may be expected around or just below the water solubility, which supports the test data available.

Consequently, RAC does not agree, based on a weight-of-evidence approach, with the DS to remove the aquatic classification Aquatic Acute 1, H400 and Aquatic Chronic 1, H410. Due to the uncertainties associated with the data indicating toxicity below the threshholds indicated in CLP, it is not possible to define the M-factors to the existing classification.

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).