Committee for Risk Assessment

RAC

Annex 1
Background document
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

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

15 March 2017

CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2

Substance Name:

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

EC Number: 404-360-3

CAS Number: 119313-12-1

Index Number: 606-047-00-9

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Industry in accordance with Article 37(6) of the CLP Regulation

Version number: 1 **Date: May 2016**

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PART A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	*2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone*
EC number:	*404-360-3*
CAS number:	*119313-12-1*
Annex VI Index number:	*606-047-00-9*
Degree of purity / Impurities:	*98 – 99.9 % as a racemate* *0.2 % α-Benzyl-α-(dimethylamino)-3-chloro-4`-morpholinobutyrophenone* *Four other known impurities at less than 0.1 or 0.05 %. Sum of unspecified impurities < 0.05 %*

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation
Current entry in Annex VI, CLP Regulation (as of May 2016)	Aquatic Acute 1 H400 – Very toxic to aquatic life. Aquatic Chronic 1 H410 – Very toxic to aquatic life with long lasting effects.
Current proposal for consideration by RAC	No classification for environment
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	No classification for environment

1.3 Proposed harmonised classification and labelling based on CLP Regulation

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives				Conclusive but not sufficient for classification
2.2.	Flammable gases				Conclusive but not sufficient for classification
2.3.	Flammable aerosols				Conclusive but not sufficient for classification
2.4.	Oxidising gases				Conclusive but not sufficient for classification
2.5.	Gases under pressure				Conclusive but not sufficient for classification
2.6.	Flammable liquids				Conclusive but not sufficient for classification
2.7.	Flammable solids				Conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures				Conclusive but not sufficient for classification
2.9.	Pyrophoric liquids				Conclusive but not sufficient for classification
2.10.	Pyrophoric solids				Conclusive but not sufficient for classification
2.11.	Self-heating substances and mixtures				Conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases				Conclusive but not sufficient for classification
2.13.	Oxidising liquids				Conclusive but not sufficient for classification
2.14.	Oxidising solids				Conclusive but not sufficient for classification
2.15.	Organic peroxides				Conclusive but not sufficient for classification
2.16.	Substance and mixtures corrosive to metals				Conclusive but not sufficient for classification
3.1.	Acute toxicity - oral				Conclusive but not sufficient for classification
	Acute toxicity - dermal				Conclusive but not sufficient for classification
	Acute toxicity - inhalation				Data lacking

3.2.	Skin corrosion / irritation				Conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation				Conclusive but not sufficient for classification
3.4.	Respiratory sensitisation				Data lacking
3.4.	Skin sensitisation				Conclusive but not sufficient for classification
3.5.	Germ cell mutagenicity				Conclusive but not sufficient for classification
3.6.	Carcinogenicity				Data lacking
3.7.	Reproductive toxicity	Repr. 2, H361d (part of previously submitted proposal for harmonized C&L)		None; but a CLH dossier for inclusion of Repr. 2, H361d was initially submitted to ECHA in December 2014; a revised version was submitted in August 2015	
3.8.	Specific target organ toxicity –single exposure				Conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure				Conclusive but not sufficient for classification
3.10.	Aspiration hazard				Conclusive but not sufficient for classification
4.1.	Hazardous to the aquatic environment	No classification		Aquatic Acute 1 Aquatic Chronic 1	Conclusive but not sufficient for classification
5.1.	Hazardous to the ozone layer				Conclusive but not sufficient for classification

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

2 BACKGROUND TO THE CLH PROPOSAL

The dossier was prepared by industry according to Article 37(6) of the CLP Regulation.

2.1 History of the previous classification and labelling

The substance was registered as ELINCS at the national British authority in 1990. The substance showed aquatic toxicity and was not readily biodegradable resulting in a legal classification for danger to the environment (N; R50/53) under directive 67/548/EEC, 25th ATP. The EC-name of the substance was added to Annex I with a typing error. Specifically, the dash after the number four was left out and the name is currently incorrectly given as *2-benzyl-2-dimethylamino-4-morpholinobutyrophenone.* With the introduction of EC Regulation 1272/2008, the classification was translated into the hazard class 1 for both acute and chronic aquatic toxicity. No need for classification and labelling was derived from the experimental data on acute oral and dermal toxicity, subacute oral toxicity, genotoxicity in vitro, irritation and skin sensitization.

The testing requirements for the tonnage level of >100 tpa as issued by UK HSE in 2008 consisted of a one-generation study (OECD 415), environmental studies and information related to the risk assessment. The results of the one generation study triggered submission of a proposal for harmonized classification and labelling to ECHA by BASF SE in December 2014. By that time all finalized experimental data on environmental hazards were consistent with the existing classification and labelling. Since then new experimental data on aquatic toxicity has become available showing that the existing harmonized classification and labelling for aquatic toxicity needs to be changed.

For the purpose of this CLH proposal all registration dossiers available in REACH-IT in December 2015 have been considered by the German CA.

2.2 Short summary of the scientific justification for the CLH proposal

The current classification is based on old acute toxicity data. Since 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone is not readily biodegradable and the older studies on the acute toxicity to fish, Daphnia and algae revealed LC_{50} and EC_{50}-values between 0.46 and 4 mg/L a classification for environmental hazards (Aquatic Acute 1 and Aquatic Chronic 1) was considered to be appropriate.

From a scientific present-day perspective the studies show various deficiencies and are regarded as not reliable:

The study on the acute toxicity to fish was conducted using high concentrations of emulsifier. 244 mg l-methyl-2-pyrrolidon and 1 mg alkylphenol-polyglykol-ether per litre water were used for the highest test concentration. Therefore, the concentration of the emulsifier exceeds the maximum amount recommended within the OECD-guideline 203. Additionally, a deposit was observed after 24 h in all test concentrations except in the lowest test concentration.
The study on the acute toxicity to aquatic invertebrates was also conducted by using an emulsifier which exceeded the recommended concentration by far. Additionally, small parts of the test substance were swimming at the surface of the test solution at a nominal concentration of 100 mg/L from the start of the test and at 18-100 mg/l after 24 h exposure. A slight deposit was observed at nominal concentrations from 58-100 mg/L after 24 h exposure. Furthermore, the test duration was 24 h instead of 48 h.
The third toxicity study on aquatic algae was considered not reliable as well. The study was only conducted according to an internal protocol of the test facility and not according to OECD guideline. Acetone was used as solvent. Additionally, precipitation of the test substance at 10 mg/L was

observed at the beginning of the tests and the results for the growth rate are not given. However, after 72 h no precipitate was observed in any of the solutions.

In the meantime, chronic toxicity studies to fish (OECD 210) and aquatic invertebrates (OECD 211), a new study on the toxicity to aquatic algae (OECD 201) and, additionally a new study on the acute toxicity to fish (OECD 203) have been conducted. All studies revealed no toxic effects up to the limit of solubility within the test media. However, the long-term toxicity study on fish (OECD 210) is not reliable and will not be used for classification and labelling since the validity survival criteria are not met in the control group:

- Short-term toxicity to fish (OECD 203)
  LC_{50} (96 h) > 0.142 mg/L (measured); > 10 mg/L (nominal)

- Long-term toxicity to aquatic invertebrates (OECD 211):
  NOEC (21 d, *Daphnia magna*, reproduction, immobilization and length of parental daphnids) ≥ 0.21 mg/L (measured); ≥ 10 mg/L (nominal)

- Toxicity to aquatic algae (OECD 201):
  ErC_{50} (72 h) > 2 mg/L (measured); > 200 mg/L (nominal)

Tab 4: Overview of data used for the classification and labelling

Endpoint	**Values used for Classification**	
	Acute classification	**Chronic classification**
Fish	LC_{50} (short-term toxicity) > max. solubility	LC_{50} (short-term toxicity) > max. solubility and low potential for bioaccumulation (logPow = 2.91)
Invertebrates	NOEC (long-term toxicity) ≥ max. solubility (since a saturated solution has been tested in the long-term toxicity study, the value can also be used to give an assessment about the acute toxicity)	NOEC (long-term toxicity) ≥ max. solubility
Algae	EC_{50} (short-term toxicity) > max. solubility	EC_{50} (short-term toxicity) > max. solubility and low potential for bioaccumulation (logPow = 2.91)

For details please refer to Part B of this document.

According to table 4.1.0 ("Classification categories for substances hazardous to the aquatic environment") of Regulation (EC) No 1272/2008, classification criteria for chronic category 2 include

(1) Non-rapidly degradable substances for which there are adequate chronic toxicity data available.

- Chronic NOEC or EC_x (for fish) ≤ 0.1 mg/L
- Chronic NOEC or EC_x (for crustacea) ≤ 0.1 mg/L
- Chronic NOEC or EC_x (for algae and other aquatic plants) ≤ 0.1 mg/L

(2) Substances for which adequate chronic toxicity data are not available

- LC_{50} / EC_{50} (fish, crustacea, algae) ≤ 1 mg/L (and the substance is not rapidly degradable and/or the experimentally determined BCF is ≥ 500 (or, if absent, the log Kow ≥ 4).

With respect to the findings of the new toxicity studies on fish, Daphnia and algae, no acute and chronic toxicity of the substance in the range of its solubility is recorded. Furthermore, due to the absence of any bioaccumulative potential, it appears appropriate to remove the classification of the substance for environmental hazards.

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

Tab 5: Current classification and labelling in Annex VI

Index -No	International Chemical Identification	EC-No	CAS -No	Classification		Labelling	
				Hazard Class and Category Code(s)	Hazard Statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)
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

2.3.2 Parallel CLH proposal for reproductive toxicity

In addition to the present proposed removal of the environmental classification for 2-benzyl-2-dimethylamino-4-morpholinobutyrophenone an additional CLH dossier with a proposal for a classification as Reproductive Toxicity Category 2 (Repr. 2; H361d) was first submitted to ECHA on 22nd December 2014 by the Industry. The final submission of said dossier took place on 17th September 2015 and the public consultation was held from 27th October to 11th December 2015. As of this date no RAC opinion on this substance regarding reproductive toxicity has been adopted.

2.4 Current self-classification and labelling

According to ECHAs brief profile substance profile there are currently 136 individual notifications for the substance in ECHAs classification and labelling inventory. While all notifiers and registrants classify the substance as Aquatic Chronic 1 as required by Annex VI of the CLP-Regulation, not all classify the substance as Aquatic Acute 1. A few (5) notifiers, as well as a joint registration dossier omit the required classification. Whether this is deliberate or due to a misinterpretation of the labelling provisions concerning the omission of hazard statement H400 in presence of H410 remains speculative. In addition to the environmental labelling required by Annex VI of the CLP-Regulation some notifiers and registrants (29) classify the substance as Reproductive Toxicity Category 2 (Repr. 2; H361).

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Currently, the substance has a harmonized classification for aquatic toxicity (CLP Annex VI index no. 606-047-00-9). Action at the Community level is required pursuant to CA/8/2013v2 to adapt the classification with newly available data on aquatic toxicity. Considering all available information the existing harmonised classification with Aquatic Acute 1 and Aquatic Chronic 1 (according to CLP) is not appropriate (see chapter 2.2). It is recommended that the classification proposal is considered for the modification of the entry in Annex VI of Regulation (EC) No 1272/2008.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

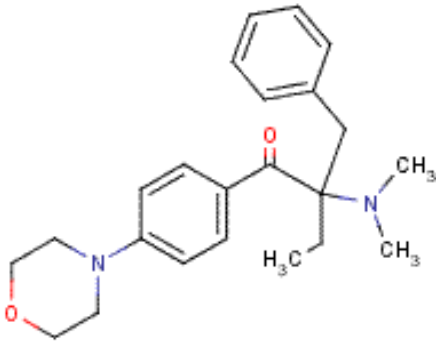
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 6: Substance identity

EC number:	404-360-3
EC name:	2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone
CAS number:	119313-12-1
CAS name:	1-Butanone, 2-(dimethylamino)-1-[4-(4-morpholinyl)phenyl]-2-(phenylmethyl)-
IUPAC name:	2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone
CLP Annex VI Index number:	606-047-00-9
Molecular formula:	C23 H30 N2 O2
Molecular weight range:	366.5

Structural formula:



1.2 Composition of the substance

Table 7: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
2-benzyl-2-dimethylamino-4'-morpholinobutyro-phenone	99.5 %	98 – 99.9 %	The substance is a racemate.

- Current Annex VI entry: Aquatic chronic 1, Aquatic Acute 1

Table 8: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
α-Benzyl-α-(dimethyl-lamino)-3-chloro-4`-morpholinobutyrophenone	0.2 %	0.01-0.2 %	

Current Annex VI entry: not relevant for C & L

Table 9: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
none				

Current Annex VI entry: not applicable

Further information regarding the composition of the substance is given in the technical dossier.

1.2.1 Composition of test material

The substance of concern is a racemic mixture with a purity range between 98 and 99.9 %.

1.3 Physico-chemical properties

Except for information on water solubility and the partition coefficient n-octanol/water, physico-chemical properties are not relevant for the purpose of this CLH report. Therefore, water solubility and the partition coefficient n-octanol/water are the only endpoint covered hereunder.

Table 10: Summary of relevant information on physico-chemical properties

Endpoint	Results	Remarks	Reference
Water solubility	5.9 mg/L	distilled water	CIBA-GEIGY Ltd (1989a)
Partition coefficient n-octanol/water (log value)	logPow= 2.91		CIBA-GEIGY Ltd. (1988a)

2 MANUFACTURE AND USES

2.1 Manufacture

The substance is manufactured outside of the EU.

2.2 Uses

2-Benzyl-2-dimethylamino-4'-morpholinobutyrophenone is used as a photosensitive agent in printing inks, pigmented coatings and photopolymers for imaging applications. These uses involve industrial and professional workers. The mechanism of photo-curing is initiated by UV-induced cleavage of the substance.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Not classified for physico-chemical properties.

4 HUMAN HEALTH HAZARD ASSESSMENT

As of October 2015, 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone has no harmonized classification and labelling for human health endpoints. Since introduction of the legal classification a one-generation-study (OECD 415) has been conducted and this study showed that the substance causes adverse effects on development. A separate CLH dossier for reproductive toxicity was submitted to ECHA in August 2015 with a proposal for Repr. 2 (H361d).

5 ENVIRONMENTAL HAZARD ASSESSMENT

5.1 Degradation

5.1.1 Abiotic degradation

5.1.1.1 Hydrolysis

A study on hydrolysis as a function of pH was conducted according to EEC directive 84/449 C.10 (CIBA-GEIGY Ltd. 1989b). The test substance is stable at pH 4 and pH 7 (less than 10 % decomposition after 5 days at 50 °C). However, the hydrolysis test could not be performed at pH 9 because the solubility of the test substance in the buffer solution at pH 9 is too low.

Table 11: Summary of relevant information on hydrolysis

Method	Results	Remarks	Reference
EEC directive 84/449 C10 equivalent or similar to OECD Guideline 111 (Hydrolysis as a Function of pH)	Recovery (in %): pH 4: 98.6 at 50 °C after 5 d pH 7: 93.8 at 50 °C after 5 d Transformation products: no	2 (reliable with restrictions) key study experimental result **Test material (EC name): 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone**	CIBA-GEIGY Ltd. (1989b)

5.1.2 Biodegradation

A test on ready biodegradability was conducted according to GLP and OECD 301B (CIBA-GEIGY Ltd. 1989c). After 28 d only 3 % biodegradation was observed. Therefore, the test substance is poorly biodegradable and not readily biodegradable (according to OECD criteria).

Table 12: Summary of relevant information on biodegradation

Method	Results	Remarks	Reference
Test type: ready biodegradability activated sludge, domestic, adapted OECD-GUIDELINE No. 301 B) (Paris 1981) equivalent or similar to OECD Guideline 301 B (Ready Biodegradability: CO2 Evolution Test)	under test conditions no biodegradation observed % Degradation of test substance: 0 after 28 d (CO2 evolution) (10 mg test substance/L) 3 after 28 d (CO2 evolution) (20 mg test substance/L)	1 (reliable without restriction) key study experimental result **Test material (EC name): 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone**	CIBA-GEIGY Ltd. (1989c)

5.2 Environmental distribution

5.2.1 Adsorption / desorption

A GLP guideline study according to OECD 106 has been conducted to determine the adsorption-coefficient of the test item (Fraunhofer-lnstitut fur Umweltchemie und Okotoxikologie 1995). The HPLC-screening method gave a logKoc of 4.69. Therefore, adsorption to solid soil phase is expected.

Table 13: Summary of relevant information on adsorption / desorption

Method	Results	Remarks	Reference
Study type: adsorption (soil) HPLC estimation method equivalent or similar to OECD Guideline 121 (Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC))	Adsorption coefficient: log Koc: 4.69	1 (reliable without restriction) key study experimental result **Test material (EC name): 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone**	Fraunhofer-lnstitut fur Umweltchemie und Okotoxikologie (1995)

5.2.2 Volatilisation

No relevant information available and not relevant for the purpose of this dossier.

5.3 Aquatic Bioaccumulation

Valid experimental data on bioaccumulation are not available. However, due to the logPow of 2.91 it can be concluded that the test substance is not bioaccumulative according to PBT-criteria. Significant accumulation in organisms is not expected.

5.4 Aquatic toxicity

Reliable data on the acute toxicity are available for aquatic algae and fish. Available studies on the acute toxicity to aquatic invertebrates are regarded as not reliable. Nevertheless, since reliable data on the long-term toxicity towards aquatic invertebrates (*Daphnia magna*) are available new tests on the acute toxicity to aquatic invertebrates will not be conducted. Additionally, effects up to the maximum solubility within the test media could neither be observed in the acute toxicity test to aquatic algae and fish nor in the long-term toxicity studies using *Daphnia magna*. The test substance is considered as not toxic to aquatic organisms. The long-term toxicity study to fish is disregarded and considered not reliable since the post-hatch survival within the control is way below the validity criteria. Therefore, this study cannot be used for classification and labelling. Instead, the results of the acute toxicity study to fish are used to derive the chronic classification. Nevertheless, since in all test concentration the overall survival was higher compared to the control and in the 100 % saturated solution no effects were observed and the validity criteria are almost met, it is not justified especially due to animal welfare reasons to conduct a second long-term toxicity study on fish. It can be assumed with sufficient confidence, that a chronic study with fish would not provide any additional information for improving the risk assessment.

5.4.1 Fish

5.4.1.1 Short-term toxicity to fish

A GLP guideline study according to OECD 203 has been conducted (DR. U. NOACK-LABORATORIEN 2014). Due to the low solubility and the light sensitivity of the test item a semi-static test with daily renewal of the Water Soluble Fraction was carried out. The loading rate of nominal 10 mg/L was chosen with regard to the expected water solubility given as 0.75 mg/L (buffer solution pH 7) and 0.03 mg/L (buffer solution pH 9), thus clearly exceeding the reported solubility values. The measured initial concentrations were within this range. Additionally, due to the light sensitivity of the test substance solutions all preparation steps were carried out under red light. The stirring phase (24 hours) and the test were done in the dark. Samples for the determination of test item analysis were handled under light exclusion.

After 96 h of exposure no effects occurred within the range of solubility and the LC_{50} was determined to be > 10 mg/L (loading rate) respectively > 0.142 mg/L (geometric mean measured). Therefore, the test substance is with high probability not acutely harmful to fish.

Furthermore, a second study on the toxicity to fish is available (Ciba AG 1988). However, the study is regarded as not reliable since test item was applied using a very high amount of emulsifier (244 mg 1-methyl-2-pyrrolidon and 1 mg alkylphenol-polyglykol-ether per liter water in the concentration used for the highest test concentration). Therefore, the concentration of the emulsifier exceeds the maximum amount recommended in the OECD guideline 203. Due to the use of emulsifier the test concentrations are all high above the water solubility. Additionally, deposit was observed after 24 h in all test concentrations except in the lowest test concentration. Moreover, the pH value (8.0 - 8.4) is at the upper limit of the recommendations in the OECD test guideline 203 and that could lead additionally to non-substance-related toxic effects.

Table 14: Overview of short-term effects on fish

Method	Results	Remarks	Reference
Danio rerio freshwater semi-static OECD Guideline 203 (Fish, Acute Toxicity Test)	LC_{50} (96 h): > 10 mg/L loading rate (nominal) based on: mortality (No acute toxic effects occur within the range of solubility.) LC_{50} (96 h): > 0.142 mg/L test mat. (meas. (geom. mean)) based on: mortality (No acute toxic effects occur within the range of solubility.)	1 (reliable without restriction) key study experimental result **Test material (EC name): 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone**	DR. U. NOACK-LABORATORIEN (2014)
Brachydanio rerio (new name: Danio rerio) static OECD-Guideline No. 203, Paris 1984	LC_{50} (96 h): 0.46 mg/L test mat. (meas. (not specified)) based on: mortality (95 % CL; The test concentration declined from 24 - 41 of the nominal	3 (not reliable) disregarded study experimental result **Test material (EC name): 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone**	Ciba AG (1988)

Method	Results	Remarks	Reference
equivalent or similar to OECD Guideline 203 (Fish, Acute Toxicity Test)	concentration at 0 h to 2-6 % of the nominal concentration at 96 h. The LC_{50} values are based on the concentrations measured after 96 h.		

5.4.1.2 Long-term toxicity to fish

A semi-static GLP guideline study according to OECD 210 has been conducted (NOTOX 1996). Due to the low solubility of the test substance within the test medium a saturated solution using 10 mg/L test substance nominal has been used. 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 disregarded for classification and labelling since 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 % (range 17 %-50 %). This was well below the acceptability criteria of > 70 % post hatch survival as prescribed by the guideline.

The relative low survival rate in the control group made it even more difficult to evaluate possible effects on survival by exposure to the test substance. However, the larvae, which were exposed to the treated solutions, all showed a higher overall survival than the controls. Furthermore, larvae which were exposed to the 100 %-filtrate had a post hatch survival at day 15 of 71.5 % (range - 81 %) and at day 29 (end of test) of 62.5 % (range 59 - 65 %), which approximates the 70 % post hatch survival.

Nevertheless, during the yolk-sac period, the larvae developed normally and no visible effects were recorded except for some malformed individuals (not test substance related).

As already indicated above during the transition period from yolk-sac phase to free feeding phase, some of the smaller larvae became totally immobile. Eventually, these immobile larvae did not survive as the test progressed. Additionally, rather large variations in both weight and length were recorded in all groups including the control group. These variations were related to differences in development rates normally seen in zebra-fish larvae. Statistical analysis of the body weights corrected for the number of surviving larvae showed no significant differences compared to the control group or among the various groups.

The NOEC after 29 d is above the solubility of the test substance.

However, the relative low survival rate in the control group at the end of the test made it difficult to evaluate any effects on survival induced by exposure to highly saturated solutions of the test substance. Nevertheless, considering the validity criterion of a minimum of 70 % post hatch survival, the relative high post hatch survival rates in the 100 % saturated test solutions indicate that the test item concentrations corresponding with maximum soluble concentrations in water do not affect embryonic or larval development significantly. Therefore, even though the test was regarded as not reliable due to the high mortality within the control group, the results can be used to show that also in fish no chronic toxicity would be expected since the survival rate in the highest test concentration (100 % filtrate and therefore maximum solubility) is very close to the validity criteria and,

additionally, higher survival rates were observed in all test concentrations compared to the control concentration.

Hence, since no difference in the long-term sensitivity of fish, daphnids and algae is expected based on the acute toxicity data on all trophic levels, no long-term effects up to the solubility limit on fish are expected either since no chronic effects occurred in the long-term tests with daphnids and algae up to the solubility limit. This is supported by the results of the 100 % saturated solution in the disregarded fish long-term toxicity study where the survival rate met almost the validation criteria and no effects occurred. Additional, especially due to animal welfare it is scientifically not justified to conduct a second new long-term toxicity test on fish since it can be assumed with sufficient confidence, that an additional chronic study with fish would not provide any additional information for improving the hazard assessment and no difference in the sensitivity of fish and daphnids are expected.

However, as already mentioned above, since the long-term toxicity study is not reliable it will not be used for classification and labelling. Instead, the short-term toxicity data on fish are used for the acute and chronic classification and labelling.

Table 15: Overview of long-term effects on fish

Method	Results	Remarks	Reference
Brachydanio rerio (new name: Danio rerio) freshwater early-life stage: reproduction, (sub)lethal effects semi-static OECD Guideline 210 (Fish, Early-Life Stage Toxicity Test)	NOEC (29 d): >= 0.1 mg/L test mat. (meas. (initial)) based on: mortality (No chronic effects within the range of solubility.) NOEC (29 d): >= 0.1 mg/L test mat. (meas. (initial)) based on: larval development (No chronic effects within the range of solubility.)	3 (not reliable) disregarded study experimental result **Test material (EC name): 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone**	NOTOX (1996a)

5.4.2 Aquatic invertebrates

1. 5.4.2.1 Short-term toxicity to aquatic invertebrates

A short-term toxicity study on *Daphnia magna* has been conducted (CIBA-GEIGY Ltd. 1988b). The test is regarded as not reliable since the test item was applied using an emulsifier (718 mg/L acetone and 3 mg/L alkylphenol-polyglykol-ether were used for the highest test concentration). Therefore, the concentration of the vehicle exceeds by far the maximum amount recommended within the OECD-guidance document (OECD SERIES ON TESTING AND ASSESSMENT Number 23). Additionally, small parts of the test substance were swimming at the surface of the test solution at conc. 100 mg/L nominal from the start of the test and at 18-100 mg/L after 24 h exposure. A slight deposit was observed at nominal concentrations of 58-100 mg/L after 24 h exposure. Furthermore, test duration was 24 h instead of 48 h.

Moreover, long-term studies were conducted using saturated solutions. Hence, the results can also be used for derivation of the acute classification.

Table 16: Overview of short-term effects on aquatic invertebrates

Method	Results	Remarks	Reference
Daphnia magna freshwater static OECD-Guideline No. 202, Paris 1984 equivalent or similar to OECD Guideline 202 (Daphnia sp. Acute Immobilisation Test)	EC_{50} (24 h): > 0.8 mg/L test mat. (meas. (not specified)) based on: mobility (No acute toxic effects within the range of solubility.)	3 (not reliable) disregarded study experimental result **Test material (EC name): 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone**	CIBA-GEIGY Ltd. (1988b)

5.4.2.1 Long-term aquatic invertebrates

A semi-static GLP guideline study according to OECD 211 has been conducted (ECT Oekotoxikologie GmbH 2009a). Due to the low solubility of the test item within the test medium a saturated solution has been used. Under the conditions of the test, the test item showed no effect on the test organisms at 100 % of the saturated solution at 10 mg/L. The mean measured concentration was determined to be 0.21 mg/L. The NOEC and LOEC values of the parameter fecundity (cumulative number of living offspring per parent animal alive at the end of the test), immobility and length of parental daphnids are all above the maximum solubility.

Therefore, the test substance is with high probability chronically not harmful to aquatic organisms.

Table 17: Overview of long-term effects on aquatic invertebrates

Method	Results	Remarks	Reference
Daphnia magna freshwater semi-static OECD Guideline 211 (Daphnia magna Reproduction Test)	NOEC (21 d): >= 0.21 mg/L test mat. (meas. (initial)) based on: reproduction NOEC (21 d): >= 0.21 mg/L test mat. (meas. (initial)) based on: immobilisation NOEC (21 d): >= 0.21 mg/L test mat. (meas. (initial)) based on: morphology (length of parental daphnids) LOEC (21 d): > 0.21 mg/L test mat. (meas. (initial)) based on: reproduction LOEC (21 d): > 0.21 mg/L test mat. (meas. (initial)) based on: immobilisation LOEC (21 d): > 0.21 mg/L test mat. (meas. (initial)) based on: morphology (length of parental daphnids)	1 (reliable without restriction) key study experimental result **Test material (EC name): 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone**	ECT Oekotoxikologie GmbH (2009a)

5.4.3 Algae and aquatic plants

One reliable GLP guideline study according to OECD 201 is available (NOTOX 1996b). Due to the low solubility of the test item saturated solutions with 100 and 200 mg/L test substance nominal were used. 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. There was a relatively high variation between the extinction values of the different replicates, including those recorded in the control replicates. Therefore it was decided to repeat the test.

Concentrations measured at the start of a second limit test ranged from 0.18 to 1.0 mg/L. 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.

Hence, based on the results of the present studies with *Selenastrum capricornutum* the test substance did not inhibit cell growth in saturated solutions with nominal concentrations far above the maximum water solubility.

The EC_{50} values for both cell growth inhibition (EbC_{50}: 0-72 h) and growth rate reduction (ErC_{50}: 0-72 h) were greater than the maximum attainable concentration of approximately 2 mg/L.

The second study (ABC Laboratories 1993) is regarded as not reliable since it was conducted as screening study and not according to OECD guideline. The test was only conducted according to an internal protocol of the test facility. Acetone was used as solvent. Additionally, precipitation of the test substance at 10 mg/L was observed at the beginning of the test and the results for the growth rate are not given. However, after 72 h no precipitate was observed in any of the solutions. Nevertheless, due to its strong deficiencies the test is regarded as not valid.

Table 18: Overview of effects on algae and aquatic plants

Method	**Results**	**Remarks**	**Reference**
Selenastrum capricornutum (new name: Pseudokirchnerella subcapitata) (algae) freshwater static OECD guideline No. 201, Adopted June 7, 1984 EU Method C.3 (Algal Inhibition test) ISO 8692 (Water Quality - Fresh Water Algal Growth Inhibition Test with Scenedesmus subspicatus and Selenastrum capricornutum) (1989)	EC_{50} (72 h): > 2 mg/L test mat. (meas. (initial)) based on: growth rate (No acute toxic effects within the range of solubilty.) EC_{50} (72 h): > 2 mg/L test mat. (meas. (initial)) based on: biomass (No acute toxic effects within the range of solubilty.)	1 (reliable without restriction) key study experimental result **Test material (EC name): 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone**	NOTOX (1996b)
Scenedesmus subspicatus (new name: Desmodesmus subspicatus) (algae) freshwater static ABC Protocol No. 9207	EC_{50} (72 h): 4 mg/L test mat. (estimated) based on: growth rate (95 % CL=3.1 and 4.9 mg/L) NOEC (72 h): 0.1 mg/L test mat. (nominal) based on: growth rate	3 (not reliable) supporting study experimental result **Test material (EC name): 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone**	ABC Laboratories (1993)

5.4.4 Other aquatic organisms (including sediment)

No data available.

5.5 Comparison with criteria for environmental hazards (sections 5.1 – 5.4)

Tab 19: Comparison with criteria for environmental hazards

	Criteria for environmental hazards	2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone	Conclusion
Rapid Degradation	Readily biodegradable in a 28-day test for ready biodegradability	≤ 3 % CO_2 evolution in 28 days	**Not rapidly biodegradable**
Bioaccumulation	BCF ≥ 500 Log Kow ≥ 4	Log Kow = 2.91	**Not bioaccumulative**
Aquatic Toxicity	Acute toxicity data: $LC_{50}/EC_{50}/ErC_{50}$ ≤ 100 mg/L Chronic toxicity data: NOEC ≤ 1mg/L	Fish: LC_{50} > 10 mg/L (loading rate, no acute effects within the range of solubility in the test medium) Invertebrates: NOEC 21d ≥ 0.21 mg/L (no chronic effects within the range of solubility in the test medium) Algae: ErC_{50} 72h > 2 mg/L (no effects within the range of solubility in the test medium) Water solubility (in distilled water) = 5.9 mg/L	**No acute and chronic toxicity within the range of solubility**

5.6 Conclusions on classification and labelling for environmental hazards (sections 5.1 – 5.4)

With respect to the findings of the acute and chronic experimental studies, no toxicity of the substance in the range of its solubility has been recorded. In all trophic levels no toxic effects occurred up to the limit of solubility in the respective test media. Therefore, the test substance is with high probability not toxic to aquatic organisms.

Furthermore, the substance does not have a significant potential to bioaccumulate which is further proof, that the test item does not have the potential to be chronically toxic to aquatic organisms.

Therefore, since the test substance shows no toxic effects within the range of solubility and is not bioaccumulative due to the logKow of 2.91 the classification with Aquatic chronic 4 according to Regulation (EC) No 1272/2008 is not justified anymore.

In conclusion, none of the criteria of Regulation (EC) No 1272/2008 have been met. Therefore, it is proposed that the substance is no longer classified for environmental hazards.

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.

Additional key elements

There is not enough reliable data available to assess the aquatic toxicity of BDMBP. In order to get more data to evaluate the DS's proposal to remove the environmental classification, QSAR calculations using ECOSAR v1.11 were performed by RAC. The results of both class-specific calculation for aliphatic amines and baseline calculation were done. ECOSAR v1.11 does not recognise aromatic amines as a separate class. The results are presented in the tables below.

Table Class-specific estimation results from ECOSAR v1.11 (melting point 113.2 °C, water solubility 5.9 mg/L given, log Kow of 4.502 estimated by ECOSAR)

ECOSAR Class	Organism	Duration	End point	Predicted mg/L	Domain (1	Endpoint specific cut-off log Kow(2	Coefficient of Determination R^2	n (3
Aliphatic amines	Fish	96 h	LC50	1.598	log kow 5, max molecular weight 1000	6.0	0.7939	90+32

[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.

Aliphatic Amines	Daphnid	48 h	LC50	0.255	log kow 5, max molecular weight 1000	5.0	0.7634	24+20
Aliphatic Amines	Green algae	96 h	EC50	0.118	log kow 6.4, max molecular weight 1000	7.0	0.7788	35+11
Aliphatic Amines	Fish		ChV(4	0.038	log kow 8, max molecular weight 1000	8.0	0.977	3+1
Aliphatic Amines	Daphnid		ChV(4	0.028	log kow 8, max molecular weight 1000	8.0	0.8023	5+2
Aliphatic Amines	Green Algae		ChV(4	0.048	log kow 5, max molecular weight 1000	7.0	0.8288	13+7

(1 Limitations: if the compound is solid and the ChV exceeds the water solubility by 10x, no effects at saturation are expected
(2 If the log Kow is greater than the endpoint specific cut-off, then no effects at saturation are ecpected for those endpoints.
(3 n = number of studies used in equation development+(log cut-off and/or SAR data not included in Regression Equitation)
(4 ChV (Chronic Value) is the geometric mean between LOEC and NOEC. If LOEC not available NOEC can be used alone.

Table. Neutral organic SAR (Baseline toxicity) for BDMBP

Organism	End point	Predicted mg/L
Fish	96 h LC50	1.704
Daphnid	48 h LC50	1.219
Green algae	96 h EC50	2.361
Fish	ChV	0.219
Daphnid	ChV	0.226
Green algae	ChV	1.034

The domain conditions are fulfilled for the estimation using ECOSAR Class Aliphatic amines. It seems that the substance may have a more specific mode of toxicity beyond the baseline toxicity. There is no measured data on the substance available in the training set of the ECOSAR QSAR. The predictive accuracy based on the r^2 values of the model seems to be acceptable.

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 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

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."

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.

6 OTHER INFORMATION

Not applicable

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