Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

2-(dimethylamino)-2-[(4-methylphenyl)methyl]-1-[4-(morpholin-4-yl)phenyl]butan-1-one

EC Number: 438-340-0
CAS Number: 119344-86-4

CLH-O-0000007134-80-01/F

Adopted

2 June 2022

P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

2 June 2022

CLH-O-0000007134-80-01/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-(dimethylamino)-2-[(4-methylphenyl)methyl]-1-[4-(morpholin-4-yl)phenyl]butan-1-one**

EC Number: **438-340-0**

CAS Number: **119344-86-4**

The proposal was submitted by **Austria** and received by RAC on **16 June 2021.**

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

PROCESS FOR ADOPTION OF THE OPINION

Austria 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 **20 September 2021**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **19 November 2021**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Michal Martínek**

Co-Rapporteur, appointed by RAC: **Irina Karadjova**

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 **2 June 2022** by **consensus**.

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

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	TBD	2-(dimethylamino)-2-[(4-methylphenyl)methyl]-1-[4-(morpholin-4-yl)phenyl]butan-1-one	438-340-0	119344-86-4	Repr. 1B Aquatic Acute 1 Aquatic Chronic 1	H360FD H400 H410	GHS08 GHS09 Dgr	H360FD H410		M = 1 M = 1	
RAC opinion	TBD	2-(dimethylamino)-2-[(4-methylphenyl)methyl]-1-[4-(morpholin-4-yl)phenyl]butan-1-one	438-340-0	119344-86-4	Repr. 1B Aquatic Acute 1 Aquatic Chronic 1	H360Df H400 H410	GHS08 GHS09 Dgr	H360Df H410		M = 1 M = 1	
Resulting Annex VI entry if agreed by COM	TBD	2-(dimethylamino)-2-[(4-methylphenyl)methyl]-1-[4-(morpholin-4-yl)phenyl]butan-1-one	438-340-0	119344-86-4	Repr. 1B Aquatic Acute 1 Aquatic Chronic 1	H360Df H400 H410	GHS08 GHS09 Dgr	H360Df H410		M = 1 M = 1	

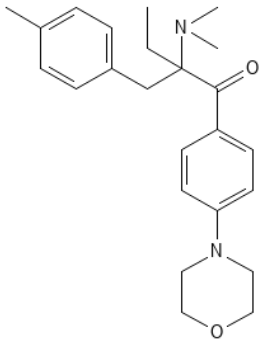
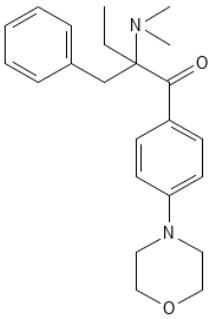
GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

2-(dimethylamino)-2-[(4-methylphenyl)methyl]-1-[4-(morpholin-4-yl)phenyl]butan-1-one is a photo initiator used in formulation of UV inks for digital printing and preparations containing the photo initiator. There is wide dispersive indoor use by professional workers in UV inks and professional application of coatings and inks.

Read across

2-(dimethylamino)-2-[(4-methylphenyl)methyl]-1-[4-(morpholin-4-yl)phenyl]butan-1-one (EC 438-340-0), also known under the trade name Omnirad 379, is a photo initiator from the group of alpha amino ketones. A closely structurally related photo initiator Omnirad 369 (EC 404-360-3) was evaluated by RAC in 2016 and a harmonised classification as Repr. 1B; H360D was agreed mainly based on an increase in stillborn pups and postnatal mortality in a one-generation study. No classification was agreed for fertility. The dossier submitter (DS) for Omnirad 379 proposed read across from Omnirad 369 to Omnirad 379 for developmental toxicity but not for fertility. The structures of both substances are shown below; the only difference is that Omnirad 379 has an extra methyl group on one of the aromatic rings.

Structures of Omnirad 379 and Omnirad 369	
	
Omnirad 379	Omnirad 369
CAS no. 119344-86-4	CAS no. 119313-12-1
EC no. 438-340-0	EC no. 404-360-3
2-(dimethylamino)- 2-[(4-methylphenyl)methyl]-1- [4-(morpholin-4-yl)phenyl]butan-1-one	2-benzyl-2-dimethylamino-4'- morpholinobutyrophenone
Read across: target substance	Read across: source substance

RAC notes that the substances have very similar structures and similar toxicological profiles: low acute toxicity, do not cause significant local effects, non-genotoxic, target organs are liver and kidney, and both cause increased postnatal mortality. However, only Omnirad 379 was found to cause testicular degeneration in the available studies.

Given the close structural similarity and also toxicological similarity between the two substances for most endpoints, RAC agrees to use the studies with Omnirad 369 as supporting information in the classification of Omnirad 379. The read across should be applied consistently for both fertility and development. As to STOT RE, relevant effects of both substances are broadly similar and consideration of the repeated dose studies with Omnirad 369 has no significant impact on the assessment.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of specific target organ toxicity – repeated exposure (STOT RE)

Summary of the Dossier Submitter's proposal

The dataset for Omnirad 379 comprises two short-term oral studies in rats: a 28-d study according to OECD TG 407 and a Reproduction/Developmental Toxicity Screening Test according to OECD TG 421, both according to GLP. The DS briefly discussed effects on haematology, liver and spleen. They did not consider the observed effects sufficient for classification.

Comments received during consultation

Comments were received from three Member State Competent Authorities (MSCAs), all in support of no classification.

Assessment and comparison with the classification criteria

28-d oral study in rats with Omnirad 379 (Anonymous, 2002a)

Wistar Han rats (HanBrl:WIST, 5/sex/group) were administered Omnirad 379 in polyethylene glycol (PEG) via oral gavage at dose levels of 0, 15, 50, 150 and 450 mg/kg bw/d. Recovery after 14 days was investigated in an additional cohort of animals (5/sex/group at 0 and 450 mg/kg bw/d). The effects at the top dose included reduced body weight (by 11%/14% in males (m)/females (f)), increased liver weight (relative, by 29%/61% in m/f), renal tubular hyaline change in males and a slight anaemia (haemoglobin reduction < 10%). These effects occurred above the extrapolated guidance value for a 28-d study (300 mg/kg bw/d) and are therefore not considered relevant for classification. Changes in male reproductive organs are presented under reproductive toxicity.

Effects at the next lower dose of 150 mg/kg bw/d included increased liver weight (relative, by 16%/15% in m/f) and increased severity of hyaline change in males (no histopathological changes in the kidneys of females). The increase in liver weight at this dose was relatively mild and not accompanied by histopathological findings or clinical chemistry changes. Kidney findings are presented in the table below. Hyaline change in male rats may be related to accumulation of alpha$_{2u}$-globulin, which is a rodent-specific phenomenon. Although special staining was not performed, the occurrence in males only represents a strong indication in this direction.

28-d study in rats with Omnirad 379: kidney findings in males							
Dose (mg/kg bw/d)	**0**	**15**	**50**	**150**	**450**	**0 recovery**	**450 recovery**
Terminal body weight (g)	297	296	296	279	265**	350	313**
Kidney weight, absolute (g)	2.02	2.14	2.08	2.20	2.30	2.39	2.22
Kidney weight, relative (%)	0.68	0.72	0.70	0.79**	0.87**	0.69	0.71
Kidney, tubular hyaline change; incidence (mean severity)	4 (1.0)	3 (1.3)	4 (2.0)	5 (2.8)	5 (3.4)	2 (2.0)	5 (2.4)

Statistically significant difference from control: *, $p \leq 0.05$; **, $p \leq 0.01$

Severity grades: 1 = minimal, 2 = slight, 3 = moderate, 4 = marked, 5 = severe

OECD TG 421 study in rats with Omnirad 379 (Anonymous, 2013b)

Wistar Han rats (Crl:WI(Han), 10/sex/group) were administered Omnirad 379 in PEG via oral gavage at dose levels of 0, 20, 60 and 200 mg/kg bw/d. Males were exposed for 28 days, females for 42-52 days. Toxic effects at the top dose included clinical signs (e.g.; piloerection), a mild body weight reduction (< 10%), changes in testes and epididymides (presented under reproductive toxicity), kidney toxicity (marked glomerular and tubular necrosis) in one female and thymus atrophy in two females. It is noted that only reproductive organs were weighed, and only reproductive organs and gross lesions were examined histopathologically, so the information for assessment of target organ toxicity is limited.

Dose selection was based on a 14-d range-finding study (Anonymous, 2013a), in which 4 females per group were exposed to 0, 150 or 300 mg/kg bw/d of Omnirad 379. The top dose animals showed clinical signs (hunched posture, piloerection), body weight loss (2 out of 4 animals), reduced food consumption and increased liver weight.

Repeated dose studies with Omnirad 369

In a 14-d study (Anonymous, 1989a) Sprague-Dawley rats (5/sex/group) were administered Omnirad 369 via oral gavage at 0, 100, 300, 1000 and 3000 mg/kg bw/d. Effects at 300 mg/kg bw/d included increased liver weight in both sexes (absolute, by 24%/43% in m/f) and increased cholesterol in females. Mortality occurred in females at the two highest doses (1 and 3 animals at 1000 and 3000 mg/kg bw/d, respectively), other effects at these doses included reduced body weight and increased liver and adrenal weight. Histopathological examination was not performed.

In a subsequent 28-d study (Anonymous, 1989b) Sprague-Dawley rats (5/sex/group) were administered Omnirad 369 via oral gavage at 0, 10, 100 and 500 mg/kg bw/d. The weights of the liver, kidneys and adrenals were increased at the top dose without corresponding histopathological findings.

In another 28-d study (Anonymous, 2009) Wistar rats (5/sex/group) were administered Omnirad 369 via oral gavage at 0, 100 and 500/250 mg/kg bw/d. The top dose group started at 500 mg/kg bw/d, but the dose level had to be reduced to 250 mg/kg bw/d due to excessive toxicity; thus, 9 days at 500 mg/kg bw/d were followed by a 5-d recovery and a 28-d treatment at 250 mg/kg bw/d. Histopathological examination showed hyaline droplets in males, hepatocellular hypertrophy in both sexes and bone marrow atrophy in both sexes at the top dose. Absolute liver weight was increased by 13%/20% (m/f) and 25%/46% (m/f) at the mid- and top dose, respectively.

Conclusion

The main target organ effects below the (extrapolated) guidance values for classification in the available studies with Omnirad 379 were a modest increase in liver weight (without a histopathological correlate or clinical chemistry changes) and a moderate tubular hyaline change in males (not in females), probably representing accumulation of alpha$_{2u}$-globulin. RAC agrees that these effects are not of sufficient toxicological significance or severity to meet the classification criteria for STOT RE. Consequently, RAC agreed with the DS's proposal that **no classification for STOT RE is warranted**.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Adverse effects on sexual function and fertility

The DS presented two studies with Omnirad 379 in rats: a 28-d study and an OECD TG 421 study, both showing testicular effects. The DS noted that no changes in reproductive organs were observed in studies with the read across source substance Omnirad 369 up to high doses. Still, the DS proposed classification in Category 1B for adverse effects on sexual function and fertility based on the studies with Omnirad 379 itself.

Adverse effects on development

The DS proposed classification for adverse effects on development in Category 1B based on stillborn pups, early postnatal mortality and reduced pup weight in the OECD TG 421 study with Omnirad 379 and in a 1-generation study with the read across source substance Omnirad 369. Classification of Omnirad 369 as Repr. 1B; H360D was agreed by RAC in 2016.

Effects on or via lactation

The DS mentioned that many of the pups that died in the OECD TG 421 study with Omnirad 379 had no milk in the stomach but acknowledged that this finding cannot be unequivocally attributed to lactation as it may as well represent developmental or maternal toxicity. Consequently, they proposed no classification for effects on or via lactation.

Comments received during consultation

Comments were received from four MSCAs.

As to fertility, all four commenting MSCAs pointed out the lack of testicular toxicity in studies with the source substance Omnirad 369. Two MSCAs also mentioned absence of effects on fertility in the OECD TG 421 study with Omnirad 379; one of them preferred Category 2 for fertility and one did not support Category 1B. Of the other two MSCAs, one supported the DS's proposal for Category 1B and one requested discussion.

In response to these comments, the DS clarified that their proposal for Category 1B was based on studies with Omnirad 379 itself, without applying a read across from Omnirad 369. Further, they stated that the absence of effect on fertility index does not decrease the concern because rats have a higher sperm reserve than humans. They retained their initial position of Category 1B for fertility.

Regarding developmental toxicity, two MSCAs supported Category 1B and another MSCA requested discussion on the role of maternal toxicity in the pup mortality. One MSCA proposed no classification for development as they considered the pup mortality secondary to maternal toxicity.

The DS replied that pup mortality could possibly be attributed to maternal toxicity only in one of the dams in the OECD TG 421 study with Omnirad 379. They further referred to the RAC opinion on Omnirad 369 where RAC concluded that the stillbirths and postnatal mortality in the 1-generation study with Omnirad 369 were unlikely to be secondary to maternal toxicity.

One MSCA supported no classification for adverse effects on or via lactation.

Assessment and comparison with the classification criteria

Adverse effects on sexual function and fertility

28-d oral study in rats with Omnirad 379 (Anonymous, 2002a)

Wistar Han rats (HanBrl:WIST, 5/sex/group, 7 weeks old at the beginning of treatment) were administered Omnirad 379 in PEG via gavage at dose levels of 0, 15, 50, 150 and 450 mg/kg bw/d. Recovery after 14 days was investigated in an additional group of animals (5/sex/group at 0 and 450 mg/kg bw/d). General toxicity in top dose males included occasional piloerection, reduced body weight (by 11% on day 28) and body weight gain (by 29% days 1-28; 96 g vs 136 g), mild anaemia, hyaline change in renal tubules, and an increase in liver weight (relative, by 29%) associated with hypertrophy and clinical chemistry changes (increased bilirubin, cholesterol and triglycerides).

Top dose males had markedly reduced testes weight (absolute, by 49%; relative, by 43%). Histopathological examination revealed testicular degeneration/atrophy, not reversible by the end of the 2-week recovery period. No testicular effects were found at the next lower dose of 150 mg/kg bw/d.

28-d study in rats with Omnirad 379: testicular findings							
Dose (mg/kg bw/d)	**0**	**15**	**50**	**150**	**450**	**0 recovery**	**450 recovery**
No. of animals per group	5	5	5	5	5	5	5
Initial body weight [a] (g)	199	189	199	193	201		
Body weight gain days 1-28 [a] (%)	68	72	64	60*	48**		
Terminal body weight (g)	297	296	296	279	265**	350	313**
Testes weight, absolute (g)	3.66	3.32	3.33	3.49	1.87**	3.73	2.14**
Testes weight, relative (%)	1.23	1.12	1.12	1.25	0.70**	1.07	0.68**
Testes, tubular atrophy; incidence (mean severity)	0	0	0	0	1 (4.0)	0	4 (2.8)
Testes, spermatic giant cells	0	0	0	0	3 (3.0)	0	1 (1.0)
Testes, reduced spermatogenesis	0	0	0	0	5 (3.8)	0	4 (4.0)
Epididymides weight, absolute (g)	1.06	1.05	1.00	0.96	0.70**	1.26	0.72**
Epididymides weight, relative (%)	0.36	0.36	0.34	0.34	0.27**	0.36	0.23**
Epididymides, cellular debris	0	0	0	0	4 (2.8)	0	5 (1.6)
Epididymides, reduced spermatozoa	0	0	0	0	4 (5.0)	0	4 (5.0)

Statistically significant difference from control: *, $p \leq 0.05$; **, $p \leq 0.01$

Severity grades: 1 = minimal, 2 = slight, 3 = moderate, 4 = marked, 5 = severe

[a] The values in columns "0" and "450" include recovery animals.

OECD TG 421 study in rats with Omnirad 379 (Anonymous, 2013b)

Wistar Han rats (Crl:WI(Han), 10/sex/group, approximately 11 weeks old at the beginning of treatment) were administered Omnirad 379 in PEG via gavage at dose levels of 0, 20, 60 and 200 mg/kg bw/d. Males were treated for 28 days (two weeks prior to mating, throughout mating and until termination), females for 42-52 days (two weeks prior to mating, throughout mating and gestation and until termination after at least 3 days of lactation). Top dose selection was based on a limited 14-d range-finding study in females, where 300 mg/kg bw/d caused clinical signs and body weight loss. The top dose selected for the main study was 200 mg/kg bw/d; top dose males showed reduced body weight (by 7% at termination) and body weight gain (by 45%).

Absolute testes weight was unaffected, absolute epididymides weight was decreased by 17% at 200 mg/kg bw/d. Histopathological examination of the testes showed germ cell exfoliation without degeneration (5 animals minimal, 3 slight, 1 moderate). Cell debris (minimal to moderate) and oligospermia (minimal to slight) were observed in the epididymides. Spermatogenic staging profiles were normal for all males. No reduction in fertility was detected.

OECD TG 421 study with Omnirad 379: parameters related to male fertility				
Dose (mg/kg bw/d)	**0**	**20**	**60**	**200**
No. of animals per group	10	10	10	10
Initial body weight (g)	327	327	326	331
Body weight gain (%)	20	19	15**	11**
Terminal body weight (g)	390	383	371*	362**
Testes weight, absolute (g)	3.64	3.49	3.74	3.45
Testes weight, relative (%)	0.93	0.91	1.01*	0.95
Testes, exfoliating germ cells; incidence (mean severity)	0	0	0	9 (1.6)
Epididymides weight, absolute (g)	1.21	1.13	1.16	1.00**
Epididymides weight, relative (%)	0.31	0.30	0.31	0.28*
Epididymides, cell debris (mean severity)	0	0	0	8 (1.8)
Epididymides, oligospermia (mean severity)	0	0	0	4 (1.3)
Fertility index [a] (%)	80	100	90	100

Statistically significant difference from control: *, $p \leq 0.05$; **, $p \leq 0.01$

Severity scores: 1 = minimal, 2 = slight, 3 = moderate

[a] females pregnant / females paired x 100

One-generation study in rats with Omnirad 369 (Anonymous, 2011)

Wistar rats (20/sex/group, 5 weeks old at the beginning of treatment) were administered Omnirad 369 in PEG via oral gavage at 0, 30, 100 and 300 mg/kg bw/d. The pre-mating period was at least 74 days. Top dose males showed increased weight of the liver (relative, by 34%) and kidneys with histopathological correlates (hepatocellular hypertrophy, eosinophilic droplets in the kidney) and also increased adrenal weight. Top dose selection was based on a 28-d range-finding study (Anonymous, 2009) where 500 mg/kg bw/d caused excessive toxicity (hunched posture, piloerection, lean appearance, retching, gasping, body weight loss or reduced weight gain).

No histopathological findings were observed in the reproductive organs of top dose males or females. Absolute testes weight was slightly increased (by 7%), prostate weight decreased (absolute and relative by 20% and 15%, respectively). Fertility-related parameters (such as fertility index) showed no significant alterations. Sperm parameters were not investigated.

One-generation study with Omnirad 369: fertility-related parameters					
Dose (mg/kg bw/d)	**0**	**30**	**100**	**300**	**HCD**
Males placed with females	20	20	19	20	
Males that did not mate	0	0	0	0	
Females pregnant	19	19	20 [a]	17	
Females not pregnant	1	1	0	3	
Male fertility index (%)	95	95	100	85	84-100
No. of implantation sites (±SD)	11.6 (±3.3)	10.9 (±3.4)	10.6 (±4.3)	10.6 (±3.8)	
Testes weight, absolute (% of control)	-	98	100	107*	
Testes weight, relative (% of control)	-	103	103	113*	
Epididymides weight, absolute (% of control)	-	97	100	100	
Epididymides weight, relative (% of control)	-	102	102	106	
Prostate weight, absolute (% of control)	-	97	100	80*	
Prostate weight, relative (% of control)	-	102	102	85*	
Seminal vesicle weight, absolute (% of control)	-	97	99	87*	
Seminal vesicle weight, relative (% of control)	-	102	101	92	

* statistically significant difference from control, $p \leq 0.05$

[a] One male of the mid dose group died prior to mating. Therefore, one male of the mid dose group mated with two females of the mid dose group.

HCD = historical control data

Repeated dose studies with Omnirad 369

In a 14-d gavage study in rats (Anonymous, 1989a; 5 animals/sex/group) several females at 3000 and 1000 mg/kg bw/d were killed within several days due to a marked body weight loss. Reproductive organ weights were reportedly unaffected up to 1000 mg/kg bw/d. A decrease in testicular weight at 3000 mg/kg bw/d is mentioned in the registration dossier without further specification (male body weight was reduced by 20% at this dose). A subsequent 28-d study (Anonymous, 1989b; 5 animals/sex/group, 6 weeks old at the beginning of treatment) with a top dose of 500 mg/kg bw/d reported no macroscopic changes in reproductive organs nor alterations in their weight. Histopathological examination of reproductive organs was not performed.

Another 28-d study (Anonymous, 2009; 5 animals/sex/group, 9-10 weeks old at the beginning of treatment), a range-finding study to the 1-generation study (Anonymous, 2011), started with a top dose of 500 mg/kg bw/d but it had to be reduced to 250 mg/kg bw/d due to excessive toxicity (clinical signs, body weight loss). Histopathological examination of testes (including staging of spermatogenesis) and epididymides did not reveal any treatment related effects. There was no significant change in sperm motility, but the sensitivity was not optimal due to a low number of animals and a low control value (55%).

Conclusion on adverse effects on sexual function and fertility

The 28-d study with Omnirad 379 showed marked testicular degeneration/atrophy at 450 mg/kg bw/d in the presence of some but not excessive general toxicity. Only slight testicular effects were observed, and no fertility reduction was detected at 200 mg/kg bw/d in the OECD TG 421 study. Although the top dose in the OECD TG 421 study was lower than that of the 28-d study, 200 mg/kg bw/d still did cause some general toxicity in both sexes.

The 28-d studies and the 1-generation study with the close structural analogue Omnirad 369 did not reveal any effect on fertility index or testicular histopathology up to 300 mg/kg bw/d nor any changes in testes weight up to 500 mg/kg bw/d. No classification for fertility was agreed by RAC for this substance (RAC, 2016).

RAC agrees with the DS that the evidence of testicular toxicity in two studies with Omnirad 379 warrants classification. RAC, however, also notes that no testicular toxicity and no effect on fertility index were observed in the 1-generation study with Omnirad 369. Therefore, in a weight-of-evidence assessment, RAC concluded that **classification in Category 2 for adverse effects on sexual function and fertility is warranted**.

Adverse effects on development

OECD TG 421 study in rats with Omnirad 379 (Anonymous, 2013b)

Wistar Han rats (10/sex/group) were administered Omnirad 379 in PEG via oral gavage at dose levels of 0, 20, 60 and 200 mg/kg bw/d. Females were treated for two weeks prior to mating, throughout mating and gestation and until termination after at least 3 days of lactation. Transient piloerection and hunched posture after dosing were occasionally observed in several top dose females, food consumption during gestation and lactation was reduced compared to controls.

Two top dose females were sacrificed on lactation days (LD) 1 (dam no. 71) and 2 (dam no. 79) due to total litter loss. Dam no. 71 was lethargic and pale before sacrifice and histopathological examination showed marked glomerular and tubular necrosis of the kidneys; food consumption was comparable to other females of this group. All 13 pups from dam no. 71 were dead at first litter check. Hunched posture was noted in dam no. 79 on the two last days before sacrifice and she had a somewhat lower food consumption towards the end of gestation compared to other females in this group (gestation day (GD) 17-20: 13 g/d, other animals 17-24 g/d). Out of the 14 pups of dam no. 79, 7 were dead at first litter check and the other 7 were dead or missing on the next day. Both dams also showed lymphoid atrophy of the thymus, which may reflect a stress response. RAC agrees with the author of the study report that the total litter loss in dam no. 71 may be a result of maternal toxicity. Involvement of maternal toxicity is possible also for dam no. 79.

Pup mortality was also increased on subsequent days: 12 pups from 4 litters were found dead (6 pups) or missing (6 pups) by termination on PND 5-7 at the top dose compared to a single pup in the control group. Seven of these dead/missing pups were from dam no. 79. Additionally, significant reduction in pup body weights was noted at the top dose on days 1 (-15%) and 4 (-20%) of lactation.

OECD TG 421 study with Omnirad 379: developmental effects					
Dose (mg/kg bw/d)	**0**	**20**	**60**	**200**	**HCD [a]**
No. of pregnant females	8	10	9	10	
No. of females with total litter loss (day of total litter loss)	0	0	0	2 (days 1, 2)	
No. of living pups (no. of litters with living pups) at first litter check	92 (8)	106 (10)	98 (9)	99 (9)	
No. of dead pups (no. of affected litters) at first litter check	0	2 (2)	4 (1)	20 (2)	
Mean no. of dead pups per litter at first litter check (±SD), including dam no. 71 [b]	0.0 (±0.0)	0.2 (±0.4)	0.4 (±1.3)	2.0 (±4.4)	Mean 0.1 (±0.3) Range 0.0-4.0 P95 1.0
No. of dead pups at first litter check, dam no. 71 excluded [b]	0	2 (2)	4 (1)	7 (1)	
Mean no. of dead pups per litter at first litter check, dam no. 71 excluded (±SD)	0.0 (±0.0)	0.2 (±0.4)	0.4 (±1.3)	0.8 (±2.3)	Mean 0.1 (±0.3) Range 0.0-4.0 P95 1.0
No. of dead or missing pups (no. of affected litters) after the first litter check until termination on LD 5-7	1 (1)	0	1 (1)	12* (4)[c]	
Mean no. of dead or missing pups per litter after the first litter check until termination (±SD)	0.1 (±0.4)	0.0 (±0.0)	0.1 (±0.3)	1.2 (±2.2)	Mean 0.1 (±0.4) Range 0.0-4.0 P95 1.0
Viability index [d] (%)	99	100	99	88*	Mean 99
Maternal bw on GD 0 (g)	213	213	214	207	
Maternal bw on LD 1	243	247	244	230	
Maternal food consumption during gestation (g/d)	20	19	19	17	
Maternal food consumption during LD 1-4 (g/d) [e]	28	26	26	22*	
Pup weight LD 1 (g)	6.2	6.1	6.1	5.3*	
Pup weight LD 4 (g)	9.2	9.1	9.1	7.4*	

* statistically significant difference from control, $p \leq 0.05$

[a] same laboratory, within 3 years before the current study, around 900 litters

[b] dam with marked renal toxicity and clinical signs (lethargic, pale)

[c] 6 pups found dead, 6 pups missing; 7 of them from 1 litter (dam no. 79)

[d] no. of pups before planned necropsy / no. of pups born alive x 100

[e] the two top dose females with total litter loss excluded

One-generation study in rats with Omnirad 369 (Anonymous, 2011)

Wistar rats (20/sex/group) were administered Omnirad 369 in PEG via oral gavage at 0, 30, 100 and 300 mg/kg bw/d. Top dose females showed reduced body weight (by up to 8%) and food consumption during lactation, liver hypertrophy (relative liver weight increased by 50%), thyroid hypertrophy and a mild increase in relative kidney weight.

The number of stillborn pups at the top dose was increased above the HCD and occurred across multiple litters. Pup viability was significantly decreased between days 0 and 4. Pup weight at the top dose was reduced by 13% and 21% on days 1 and 21 respectively. The increase in stillborn pups and postnatal mortality led to classification of Omnirad 369 in Category 1B (RAC, 2016).

One-generation study with Omnirad 369: developmental effects					
Dose (mg/kg bw/d)	**0**	**30**	**100**	**300**	**HCD**
Females with implantation sites	19	19	20	17	
Implantation sites (±SD)	11.6 (±3.3)	10.9 (±3.4)	10.6 (±4.3)	10.6 (±3.8)	
Post-implantation loss (%)	18	9	20	13	
No. of litters	18	19	17	17	
No. of pups	194	190	190	162	
Litter size	10.8	10.1	11.2	9.2	9.3-12.8
No. of stillborn pups (no. of females with stillborn pups)	0	2 (1)	6 (5)	9 (8)	
% stillborn pups	0	1.0	3.2	5.6	0-4.5
Pups dead on LD 0	0	1	0	4	
Pups dead LD 1-4	0	3	3	18	
Pups dead LD 5-21	0	0	1	1	
Viability index (pups surviving LD 0-4, %)	100	98	98	86*	94-100
Maternal bw GD 0 (g)	218	218	225	209	
Maternal bw LD 0 (g)	248	246	252	232*	
Maternal bw LD 21 (g)	273	274	279	260*	
Pup bw LD 1 (g)	6.3	6.3	5.9	5.5*	
Pup bw LD 21 (g)	46.6	46.3	44.3	36.9*	

* statistically significant difference from control, $p \leq 0.05$

Conclusion on developmental toxicity

The results of the OECD TG 421 study with Omnirad 379 shows an increase in early postnatal mortality at a dose associated with maternal toxicity. The concern is increased by a similar pattern of effects (stillbirths, early postnatal mortality, decreased pup weight) being observed without marked maternal toxicity in the 1-generation study with a closely related substance, Omnirad 369, which was classified by RAC as Repr. 1B; 360D (RAC, 2016).

RAC agrees with the DS's that **classification in Category 1B for adverse effects on development is warranted**, based on pup mortality in a study with the substance itself and on pup mortality in a study with the close structural analogue Omnirad 369.

Effects on or via lactation

Increased early postnatal mortality was observed in the OECD TG 421 study with Omnirad 379 and in the 1-generation study with Omnirad 369. The OECD TG 421 study mentions no milk (in the stomach) as a necropsy observation in a number of pups that died. At the top dose of 200 mg/kg bw/d no milk is listed as necropsy observation for all 20 pups found dead at first litter check (however, at least part of them may have been stillborn) and all 6 pups from 3 litters found dead at later time points. Nevertheless, this finding might be related to either maternal toxicity (in the litters of dams no. 71 and 79, see above) or developmental toxicity. Pup mortality has already been used to justify classification in Category 1B for adverse effects on development. Therefore, RAC **agrees with the DS that no classification for adverse effects on or via lactation is warranted**.

Overall conclusion on reproductive toxicity

RAC proposes classification of Omnirad 379 as **Repr. 1B; 360Df** and agrees with the DS's proposal of no classification for effects on or via lactation.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Aquatic Acute 1; H400 (very toxic to aquatic life) with an M-factor of 1, based on the 96h-EC_{50} value of 0.24 mg/L for green alga (derived by QSAR calculations, ECOSAR version 2.0 using the class "Aliphatic Amines"), and Aquatic Chronic 1; H410 (very toxic to aquatic life with long lasting effects) with an M-factor of 1, based on the 32 d-NOEC of 0.031 mg/L for fish growth (Fathead minnow (*Pimephales promelas*)) and the substance not being rapidly degradable.

Degradation

Ready biodegradability

The DS considered the substance as not readily biodegradable based on theoretical (QSAR) estimation and experimental studies presented below.

QSAR calculation: The dossier submitter presented QSAR calculations for Omnirad 379 performed with EPI (Estimation Programs Interface) SuiteTM version 4.10 (US-EPA, 2011) program BIOWIN. The results obtained can be accepted as valid as the substance falls within the applicability domain of the model. The calculations predict that the substance does not biodegrade fast according to Biowin 1 and 2 and that is not considered to be readily biodegradable based on Biowin 5 and 6.

Experimental data: Biodegradability of the substance Omnirad 379 was investigated in a GLP study according to OECD TG 301B (Anonymous, 2002b). Results showed 7% biodegradation based on CO_2 evolution for the substance after 28 days. The substance had an inhibitory effect on activated sludge microorganisms because the biodegradation rate in the toxicity control revealed <25% starting from day 8 until the end of the test. The DS concluded that the substance

was not readily biodegradable, but rated the experimental study as of reliability 3 (Klimisch score) based on the test item toxicity towards activated sludge microorganisms.

Another ready biodegradability study for substance Omnirad 379 was performed according to OECD TG 301C (modified MITI Test (I) under GLP). Results indicated that over 28 days of incubation, the substance was considered not readily biodegradable. The DS concluded that substance Omnirad 379 was not readily biodegradable and rated the study as Klimisch 4 due to the non availability of the full study report.

BOD5/COD

Information of oxygen demand is not available.

Hydrolysis

A GLP compliant hydrolysis study was carried out according to OECD TG 111 in three buffer solutions of pH 4, 7 and 9 at a temperature of 50°C. The results of pH 4 and 7 showed no significant degradation of the test substance (<10% degradation) at 50°C. Based on this, it was concluded that the substance was hydrolytically stable under the tested temperatures and conditions.

Photochemical degradation

Photochemical degradation of the radiolabelled substance was studied in a GLP study according to OECD TG 316. Seven major photolytic degradation products were determined (M-1 to M-7). Only product M-3 was identified as 4-(4-morpholinyl)benzaldehyde (CAS 1204-86-0) by co-chromatography against reference standard. Degradation was also observed in the dark controls. 90.8% was recovered as parent at pH 4 and 88.7% was recovered as parent at pH 7 at day 14. No major degradation products were formed in the dark controls. The other major degradation products were analyzed in an additional study (see Anonymous, 2019b). The detected seven major photolytic degradation products of Omnirad 379 in water were identified using a LC-PDA-MSn (Liquid chromatographic-Photodiode array-Mass spectrometer) method (Anonymous (2019b). Oxidation, reduction, hydrolysis, cleavage and desaturation were the main degradation processes of EC 438-340-0 in aquatic conditions at pH 7. The degradation pathway was proposed in the study.

Environmental fate and other relevant information

Adsorption

Adsorption coefficient (K_{OC}) was determined by a GLP study according to OECD TG 121 "Estimation of the adsorption coefficient Koc on Soil and Sewage sludge using High Performance Liquid Chromatography (HPLC)" (Anonymous (2002e). The Log Koc was calculated using a regression curve (Log k' vs. Log Koc) and was found to be 3.5 which was equal to a Koc value of 3431. In the study the reference items covered the range of Log Koc 1.86 to Log Koc 5.63. The adsorption coefficient was also estimated to be ≥ 3067. The DS concluded that the substance was slightly mobile.

Bioaccumulation

Experimentally determined partition coefficient

Partition coefficient, n-octanol/water (Log K_{ow}) was determined according to OECD TG 117, using the HPLC method (Anonymous, 2002f). The Log Kow was determined to be 4.1 at pH 8.1 and 25°C.

Experimentally determined BCF

Only one experimental bioaccumulation study, following OECD TG 305 was available and considered by the DS as valid. (Anonymous, 2002g). The test fish *Cyprinus carpio* were exposed to a concentration of 0.03 mg/L (high exposure level) and 0.003 mg/L (low exposure level) of the test substance in a flow-through system for 28 days. The mean steady-state BCF was 755 L/Kg_{wwt} for the whole fish at the high exposure level and 684 L/Kg_{wwt} for the whole fish at the low exposure level. For both exposure levels the steady-state was reached at day 7. The mean residual rate of the test substance was 12 % in the high exposure level and 4 % in the low exposure level at day 7 of the excretion test. The BCF was not normalised to a lipid content of 5 % and a kinetic BCF (BCF_k) was not determined. No mortality was observed in the treatment groups and control group, but as the fish weight decreased during the study period toxicity, it cannot be ruled out.

Results for BCF from four QSAR model calculations were also available:

BIOWIN v4.10 (EPI Suite™) (BCF: 61.2 L/Kg);

CataLogic v5.11.17 (BCF: 407.38 L/Kg);

T.E.S.T. v4.01 (BCF: 101.39 L/Kg);

VEGA CAESAR v2.1.13 (BCF: 10 L/Kg)

The DS concluded that, as the experimental Log Kow was above 4 and the experimental BCF for fish was above the cut-off value of 500 L/kg, the substance has a potential for bioaccumulation in aquatic environments.

Acute aquatic hazard

A summary of relevant information on acute aquatic toxicity is presented in the CLH report.

Acute (short-term) toxicity to fish

One study performed on zebrafish (*Danio rerio*) according to OECD TG 203 (1992) following GLP was available for acute toxicity to fish (Anonymous, 2002h). The test was conducted under static conditions, with the suspension of test substance at nominal concentration of 100 mg/L in the test media treated in ultrasound bath for 15 min, stirred for 3 h and filtered through a membrane filter. The undiluted filtrate was tested as the only test concentration (= 0.28 mg/L) at the test start. The exposure solution was clear throughout the whole study duration. The loading rate was lower than 1 g fish/L. After 3, 24, 48, 72 and 96 hours the test organisms were observed for mortality and abnormalities. Analysis of the test concentrations was performed at the start and end of the test via HPLC. The substance concentration decreased from 0.28 mg/L at test start to 0.06 mg/L at the end of the test (0.17 mg/L mean measured based on all measurements or 0.13 mg/L geometric mean). No mortality or other visible abnormalities were determined during the test period of 96 hours.

The REACH Registrant estimated a value of 4.161 mg/L using ECOSAR version 1.11 (class not specified) (2014). An LC_{50} value of 3.05 mg/L was calculated by the DS using ECOSAR for the class "aliphatic amines", which was slightly above the water solubility of 2.8 mg/L. The model was applicable considering the substance molecular structure and Log Kow used. The DS considered the LC_{50} value of 3.05 mg/L as valid and reliable. As a result, the DS concluded that Omnirad 379 cannot be considered acutely toxic to fish, taking into account the experimentally observed lack of toxicity at highest test concentration (LC_{50} >0.13 mg/L, measured geometric mean) and QSAR LC_{50} estimations of 4.161 mg/L and 3.05 mg/L.

Acute (short-term) toxicity to aquatic invertebrates

Acute toxicity toward invertebrates (*Daphnia magna Straus*) was studied in a limit test performed according to OECD TG 202 (1984) following GLP (Anonymous, 2002i). Test concentrations were achieved by the same procedure already described for the fish acute toxicity study. For the treatment group and control group (without test medium) 20 daphnids were used, divided into two replicates of ten and loading rate was lower than one daphnia per 2 mL test solution, under static conditions. Actual substance concentrations samples were measured at the start of the test and after 48 hours by HPLC method. The measured concentration was below the limit of quantification (LOQ) of 0.0643 mg/L at the start and at the end of the test. Two organisms were immobile after 24 and 48 hours but EC_{50} could not be established as the substance could not be measured. DS considered the test as not suitable for classification purposes.

The REACH Registrants estimated a value of 0.365 mg/L for aquatic invertebrates using ECOSAR version 1.11 (class not specified) (2014).

An LC_{50} value of 0.46 mg/L for daphnids was calculated by the Dossier Submitter using ECOSAR for the class "aliphatic amines". The model was applicable considering the substance molecular structure and Log Kow used. The DS concluded that an acute toxicity EC_{50} value for the substance could not be derived experimentally and considered, instead, the estimated QSAR value of LC_{50} 0.46 mg/L as relevant and suitable for classification.

Acute (short-term) toxicity to algae or other aquatic plants

A static algae growth inhibition study on *Desmodesmus subspicatus* was conducted according to OECD TG 201 (1984) and GLP Anonymous (2002j). Five nominal concentrations (6.25 - 100 mg/L) were tested, corresponding to actually measured by HPLC test concentrations of 0.165, 0.106, 0.055, 0.028, and 0.014 mg/L. Test media was prepared as described for fish acute toxicity study and further diluted. The actual substance concentration decreased from 0.165 mg/L at the beginning of the test to 0.015 mg/L at the end of the test (0.050 mg/L mean measured based on geometric mean). No other test concentrations were determined at the end of the test. During the whole test duration, the algae cell densities in the test mediums were equal to or even higher than in the control culture. The 72h-E_rC_{50}: > 0.050 mg/L mean measured based on geometric mean was defined.

The REACH Registrants estimated a value of 0.523 mg/L using ECOSAR version 1.11 (class not specified) (2014).

An EC_{50} value of 0.24 mg/L was calculated by the Dossier Submitter by ECOSAR version 2.0 for the class "aliphatic amines". The model was applicable considering the substance molecular structure and Log Kow used. The DS considered the EC_{50} value of 0.24 mg/L as valid and reliable.

The DS concluded that the acute toxicity value derived from the experimental study can only provide the information that the EC_{50} is above 0.05 mg/L, whilst considering relevant the valid QSAR prediction. As such, the DS concluded that the EC_{50} value of 0.24 mg/L for algae estimated by ECOSAR version 2.0 leads to the classification of the substance as **Aquatic Acute 1 with an M-factor of 1.**

Long-term aquatic hazard

A summary of relevant information on chronic aquatic toxicity is presented in CLH dossier. The chronic toxicity test on fish and aquatic invertebrates have been conducted in response to an ECHA decision pursuant to Article 41 of the REACH Regulation:

https://www.echa.europa.eu/documents/10162/6d5d9fb5-5575-2b50-4f54-b8e1c0fb26d6

Chronic toxicity to fish

A chronic toxicity of substance to *Pimephales promelas* was performed according to the OECD TG 210 over a period of 32 days (Anonymous, 2019c). The test was performed in the flow-through system, test nominal concentrations 0.0550, 0.090, 0.160, 0.280 and 0.500 mg/L were prepared using 0.1 mL dimethylformamide (DMF)/L and dosed via a computer-controlled system, flow through. The study was performed with 80 fathead minnow embryos per test group, divided into four replicates of 20. The larvae and juvenile fish were fed ad libitum. On each day, the embryos and larvae were observed for survival. Effects on development, swimming behaviour and appearance were also recorded every day. At the test end all surviving fish were weighed and the individual length was measured. The actual substance concentrations were measured by Ultra Performance Liquid Chromatography system.

All conditions during the test were controlled. The embryonic survival was 98-100 % in the treatment groups up to and including the highest average measured concentration of 0.234 mg/L without any significant difference compared to the pooled controls. The post-hatch larval survival was 84 % in the pooled controls (no statistically significant difference between the solvent and blank control) at the end of exposure. Post-hatch survival for all concentrations was not statistically different from the pooled controls, although in the two highest concentrations a trend to lower post-hatch survival was observed. The post-hatch larval survival ranged between 72 and 96% at the end of exposure. The fish exposed to the test item at mean measured concentrations between 0.043 mg/L and 0.234 mg/L showed a statistically significant reduction in body weight in the range of 21-28% ($p \leq 0.05$). Fish exposed to average concentration from 0.043 mg/L onwards resulted in statistically significant reduction of body length in the range of 7-10% in a concentration dependent manner ($p \leq 0.05$). A NOEC for body weight and length was determined to be 0.031 mg/L. DS concluded that the validity criteria of the study were met although some slight deviations were observed and considered the study valid and reliable.

According to the DS, this value was supported by a QSAR estimation using class "aliphatic amines" that was performed using ECOSAR version 2.0, using a Log Kow of 4.1 and water solubility of 2.8 mg/L that derived an estimated chronic value of 0.08 mg/L. The DS consider the prediction valid and reliable, taking into account the substance molecular structure and Log Kow used.

Chronic toxicity to aquatic invertebrates

The chronic toxicity study to aquatic invertebrate *Daphnia magna* was available and conducted according to OECD TG 211 (2012) (Anonymous, 2019d). Test substance concentrations and test conditions were defined in the frame of a range finding test, followed by two other tests. In the first test (test 1), organisms were exposed over a period of 21 days at a nominal substance concentration of 0.050, 0.090, 0.160, 0.280 and 0.500 mg/L including a blank and a solvent control with 0.1 mL DMF/L, dosed via a computer-controlled system. The corresponding actual average concentrations of the substance were 0.039, 0.074, 0.125, 0.222 and 0.349 mg/L, measured by UPLC system. Validity criteria of the test 1 were met. A statistically significant increase in immobility was observed at concentrations of 0.222 and 0.349 mg/L with a mortality of 30% and 20%. Statistically significant effects on reproduction and body length were observed already at the lowest test concentration of 0.039 mg/L. In this way, no NOEC for reproduction and length were found within the range of concentrations used in test 1.

That was the reason for a second test (test 2) with nominal substance concentrations of 0.0038, 0.012, 0.039, 0.125 and 0.400 mg/L to be performed, also in a flow-through setting. The corresponding measured average concentrations were 0.0024, 0.0083, 0.028, 0.064, 0.187 mg/L, stable during the whole test. A control group of 20 daphnids divided into four groups of five species were exposed. The condition of the parental daphnids was recorded on each day. At the end of the study duration, the length of the parental daphnids was measured. Test conditions

were carefully controlled. DS concluded that the validity criteria of the test are met. Statistically significant reduction in reproduction and mortality was observed at the highest concentration of 187 µg/L. At the highest concentration of 187 µg/L a statistically significant reduction of group mean body length of nearly 13% was observed leading to a 21d-NOEC of 0.064 mg/L.

The DS concluded that a lowest NOEC value based on mortality, reproduction and growth could be established at a concentration of 0.064 mg/L based on average concentration in the final test 2 and used for substance classification. The point estimates from the 3-param. normal cumulative distribution function (CDF) revealed an EC_{10} (reproduction) value of 65 µg/L (39-108 µg/L, 95% CI).

Application of QSAR estimation using class "aliphatic amines" and input parameters: Log Kow of 4.1 and water solubility of 2.8 mg/L revealed chronic value of 0.05 mg/L. DS considered the prediction to be valid and reliable.

Chronic toxicity to algae or other aquatic plants

A 72 hour algae growth inhibition test was conducted with *Desmodesmus subspicatus* according to OECD TG 201. Supersaturated suspension of test substance (100 mg/L) was filtered and used as highest test concentration, further concentrations obtained after 1:2; 1:4; 1:8 and 1:16 dilutions. Static conditions. Measured concentrations at the test at the start are: 0.165, 0.106, 0.549, 0.0283 and 0.0142 mg/L. Highest test concentration declined at the test end to 0.015 mg/L due to substance photosensitivity. No toxicity was observed in the study up to the highest achievable test concentration of 0.05 mg/L; the 72h-NOEC was thus above or equal to 0.05 mg/L, based on geometric mean measured concentrations.

Application of QSAR estimation using class "aliphatic amines" and input parameters Log Kow of 4.1 and water solubility of 2.8 mg/L revealed chronic value of 0.09 mg/L for green algae. The DS considered the prediction to be valid and reliable taking into account that the experimentally derived NOEC value was above or equal to 0.05 mg/L. In addition, QSAR estimations with fish and daphnia were in line with the outcome of the recently conducted experimental studies.

The overall DS conclusion was that, based on valid experimental chronic toxicity data for all three trophic levels, a 32d-NOEC of 0.031 mg/L for body weight and length of *Pimephales promelas* leads to the classification of the substance as **Aquatic Chronic 1 with an M-factor of 1.**

Comments received during consultation

One MS commented on the results from chronic toxicity studies to aquatic invertebrate *Daphnia magna* rising the question why higher value of 0.064 mg/L for endpoint mortality, reproduction and growth (test 2) was preferred instead of the reproduction endpoint from test 1 that showed significant signs of toxicity at lower concentrations (<0.039 mg/L). A second comment sought clarification on the statistical significance of marginal differences in the group mean body length and reduction of length in test 1. The correctness of the three lowest test concentrations (mean measured concentrations of 39, 74 and 125 µg/L) significantly reducing the growth parameters was also raised. Finally, the MS supported the proposed classification Aquatic Acute 1 (M-factor=1) and Aquatic Chronic 1 (M-factor=1).

DS considered test 1 of the chronic toxicity to aquatic invertebrates as valid and agreed that as the effects on the reproduction endpoint were above 10% but below 20%, the NOEC could be calculated as LOEC/2, resulting in a NOEC of 0.0195 mg/L. The DS also cited the original study report, where the reductions in mean body length were statistically significant ($p \leq 0.05$) at all concentrations including the three lowest concentrations (Williams Multiple Sequential t-test Procedure was performed).

A second National Authority (NA) proposed to present lipid normalised BCFs. Concerning the ecotoxicity data, the NA emphasized that acute toxicity studies were available for fish, invertebrates and alga, with the validity criteria being met for the acute toxicity studies for fish and alga and showing no toxicity. Although the exposure concentrations in the acute toxicity study for invertebrates were not measured (<LOQ), the results were considered valid, meaning that the experimental results showed that acute effects were not observed up to the limit of maximum achievable solubility. The NA was unclear for the necessity of QSAR application and their preference for the estimation of key endpoint for the aquatic acute hazard and also required information for the limit of detection if available and discussion on substance solubility at pH>7.

DS re-calculated and presented the lipid normalisation BCF_{SSL} 821 L/kg for the high exposure level and 743f L/kg or the low exposure level. Concerning the acute aquatic invertebrates study, the DS pointed out that only LOQ was provided in the study and all results at the beginning or at the end of the study were below this value. DS considered this study not suitable for classification. Therefore, QSAR data were used.

Omnirad 379 is a weak base and solubility could be influenced by solution pH>7. DS pointed out that quantification of the substance was successful in the algae test at pH 8.0 (beginning) and 9.3 to 9.5 (end of the test) and substance was successfully measured each of four days of the test so pKa value of 6.22 should not change substance water solubility in the aquatic invertebrate test.

Assessment and comparison with the classification criteria

Comparison with the CLP criteria

Parameter	CLP criteria	Results	Conclusion
Ready biodegradation	< 70% for 28 days	exhibited an inhibitory effect on the activated sludge microorganisms.	**Not rapidly degradable**
Bioaccumulation	Log K_{ow} ≥ 4 BCF ≥ 500 L/Kg	Log K_{ow} > 4 BCF > 500 L/Kg	**Potential for bioaccumulation**
Acute toxicity	EC_{50}	EC_{50} of 0.24 mg/L for algae estimated by ECOSAR version 2.0 for the class "aliphatic amines". supported	**Aquatic Acute 1; H400, M = 1**
Chronic toxicity	NOEC	32d-NOEC of 0.031 mg/L for body weight and length of *Pimephales promelas*	**Aquatic Chronic 1; H410, M = 1**

Rapid degradability

Experiments for rapid degradability showed that the test item was not readily degradable, with QSAR calculations confirming the experimental results, with the available data on hydrolysis (Anonymous, 2002d) indicating that the half-life was above one year. The substance was photo chemically unstable and primary biodegradation is not sufficient for the assessment of rapid degradability unless it can be demonstrated that the degradation products do not fulfil the criteria for classification as hazardous to the aquatic environment. RAC agrees with the DS conclusion that the substance is not rapidly degradable.

Bioaccumulation potential

Valid experimental values are available for Kow (4.1 at pH 8.1 and 25 °C) and bioaccumulation (BCF for fish ≥ 500 L/kg), leading to the RAC and DS conclusion that the substance has a potential to bioaccumulate in the aquatic environment.

Acute aquatic hazard

RAC agrees with the DS that experimental data for acute toxicity for fish, invertebrates and algae need to be supplemented by reliable QSAR calculations as, in the RAC opinion, reliable experimental data for aquatic invertebrates are not available. Acute toxicity tests were performed for fish, invertebrates and alga. The test substance solution for these tests was prepared according to a well-defined, identical procedure, namely filtration of 100 mg/L supersaturated solution of test substance (obtained after 15 min ultrasound treatment and 3 h stirring). Experimental data for fish showed no acute toxicity at highest measured test concentration of 0.28 mg/L, obtained after filtration of test substance suspension. Toxicity studies for alga were conducted with highest test substance concentration of 0.165 mg/L and, again, no toxicity was found.

Unexpectedly, using the same procedure for aquatic invertebrates, the highest measured test substance concentration was below the limit of quantification of the analytical method (0.0643 mg/L) at the start and at the end of the test medium renewal periods. RAC agrees with the DS that these experimental results are not valid and reliable for classification.

RAC additionally assessed the applicability and reliability of results obtained by ECOSAR version 2.0. The model classified the substance as aliphatic amine and ECOSAR models have been proven to show good accuracy predicting aliphatic amines and have a sufficient number of data points and statistical measures. They are considered, thus, scientifically valid. The prediction is within the applicability domain of the model as defined by model developers in terms of physicochemical properties (based on Log Kow and MW values) and structural domain (the model is specific for aliphatic amines, and the substance is an aliphatic amine). The aliphatic amine models have an $r^2 > 0.75$, which indicates good accuracy when predicting aliphatic amines in the training set.

Furthermore, the input value for Log Kow (=4.1,) is based on a reliable experimental data and lies within the power part of the range of available LogKow values in the model for this substance (predicted Log Kow by ECOSAR = 5.05, one experimental LogKow measurement of 5.73, but study details not accessible). This provides an indication that the substance toxicity may actually be somewhat underestimated by the model. Using as input a higher Log Kow may also lead to an acute classification also based on fish, but this has not been endorsed by the RAC, in the presence of valid experimental short-term toxicity study results for fish.

In conclusion, the available aquatic short-term database (valid experimental study results for fish and algae, supplemented by a valid QSAR-derived effects value of 0.46 mg/L for aquatic invertebrates) warrants a classification as **Aquatic Acute 1 with an M-factor of 1.**

Long-term aquatic hazard

Experimental, valid for classification, chronic toxicity data are available for fish, invertebrates and algae. RAC agrees with the commenting MS and considers the experimental results for *Daphnia magna* from both tests 1 and 2 as valid. When considering the available information from the tests, RAC proposes to use an aquatic invertebrate effects value based on the EC_{10} on reproduction (= 65 µg/L, 39-108 µg/L, 95% CI), in preference of a NOEC value for the same effects endpoint. Overall, considering that the substance is not rapidly degradable and based on the lowest chronic endpoint 32 d-NOEC of **0.031 mg/L** for *Pimephales promelas* body weight

and length, RAC supports the DS and proposes to classify the substance in the category **Aquatic Chronic 1 with an M-factor of 1**.

Additional references

RAC (2016): Opinion proposing harmonised classification and labelling at EU level of 2-benzyl-2-dimethylamino-4'-morpholinobutyrophenone; CLH-O-0000001412-86-124/F. Adopted 16 September 2016

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).