Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

hexyl 2-(1-(diethylaminohydroxyphenyl) methanoyl)benzoate; hexyl 2-[4-(diethylamino)-2-hydroxybenzoyl]benzoate

EC Number: 443-860-6
CAS Number: 302776-68-7

CLH-O-0000001412-86-253/F

Adopted

30 November 2018

Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

30 November 2018

CLH-O-0000001412-86-253/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: **hexyl 2-(1-(diethylaminohydroxyphenyl)methanoyl)benzoate; hexyl 2-[4-(diethylamino)-2-hydroxybenzoyl]benzoate**

EC Number: **443-860-6**

CAS Number: **302776-68-7**

The proposal was submitted by **Germany** and received by RAC on **19 October 2017.**

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

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **14 November 2017**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **12 January 2018**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Anja Menard Srpčič**

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 **30 November 2018** by **consensus**.

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

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors 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	607-693-00-4	hexyl 2-(1-(diethylaminohydroxyphenyl)methanoyl)benzoate; hexyl 2-[4-(diethylamino)-2-hydroxybenzoyl]benzoate	443-860-6	302776-68-7	Aquatic Chronic 4	H413	-	H413	-	-	
Dossier submitters proposal	607-693-00-4	hexyl 2-(1-(diethylaminohydroxyphenyl)methanoyl)benzoate; hexyl 2-[4-(diethylamino)-2-hydroxybenzoyl]benzoate	443-860-6	302776-68-7	**Modify** Aquatic Chronic 4 to Aquatic Chronic 1	**Modify** H413 to H410	**Add** GHS 09 Wng	**Modify** H413 to H410	**-**	**Add** M = 1000	
RAC opinion	607-693-00-4	hexyl 2-(1-(diethylaminohydroxyphenyl)methanoyl)benzoate; hexyl 2-[4-(diethylamino)-2-hydroxybenzoyl]benzoate	443-860-6	302776-68-7							
Resulting Annex VI entry if agreed by COM	607-693-00-4	hexyl 2-(1-(diethylaminohydroxyphenyl)methanoyl)benzoate; hexyl 2-[4-(diethylamino)-2-hydroxybenzoyl]benzoate	443-860-6	302776-68-7							

GROUNDS FOR ADOPTION OF THE OPINION

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Hexyl 2-(1-(diethylaminohydroxyphenyl)methanoyl)benzoate; hexyl 2-[4-(diethylamino)-2-hydroxybenzoyl]benzoate is used in cosmetics and personal care products. The substance is currently listed in Annex VI of the CLP Regulation (EC) 1272/2008 with a classification for environmental hazards as Aquatic Chronic 4 – H413. The Dossier Submitter (DS) proposed to classify the substance as Aquatic Chronic 1 – H410 (M=1000) based on lack of rapid degradation and a 21 days mean measured NOEC value of 0.0001 mg/L for *Daphnia magna*.

Degradation

There was one ready biodegradability test available on the substance (OECD TG 310 F, GLP) using 30 mg/L inoculum (domestic activated sludge, non-adapted) and 100 mg/L test substance (BASF, 2001b). The test was performed at pH 7.3-7.4. After 28 days, 2–5 % O_2 consumption was observed indicating that hexyl 2-(1-(diethylaminohydroxyphenyl)methanoyl)benzoate; hexyl 2-[4-(diethylamino)-2-hydroxybenzoyl]benzoate is not readily biodegradable. The percentage degradation of the reference substance (aniline) has reached the pass level after 14 days (80-90%).

The hydrolysis of the substance was estimated by EPI Suite HYDROWIN (v2.00). At pH 8, the half-life was predicted to be 250 days and at pH 7 6.9 years.

The photochemical degradation in air was investigated using the SRC AOP v1.92, 2007 estimation tool. A rate constant of 0.0000000002252403 cm^3/molecule*sec and a half-life in the atmosphere of 1.7 hours was calculated assuming a 24 hours day and an OH-radical concentration of 5.0E+05 molecules/cm^3. Hence, if the substance will be exposed to air, it will be rapidly degraded by photochemical degradation. Nevertheless, based on estimated Henry´s law constant of 0.000019 Pa·m^3/mol it will not evaporate from water surface to air.

The DS considered hexyl 2-(1-(diethylaminohydroxyphenyl)methanoyl)benzoate; hexyl 2-[4-(diethylamino)-2-hydroxybenzoyl]benzoate as not rapidly degradable for classification purposes.

Bioaccumulation

The octanol-water partition coefficient (log K_{OW}) of 6.2 at 24°C (without adjustment of pH value) was measured by EU Method A.8 (HPLC method).

A fish bioaccumulation study (OECD TG 305, GLP) is also available. The zebrafish (*Danio rerio)* was exposed to two nominal concentrations (0.1 and 1 µg/L) of the ^{14}C-radiolabelled test substance for 28 days in a flow-through system, followed by a 16 days (1 µg/L) and 21 days (0.1 µg/L) depuration period. The concentration in the fish was found to reach steady state within 7 days for both concentration groups. A steady-state BCF of 126.8 L/kg (0.1 µg/L) and 215.4 L/kg (1 µg/L) and a kinetic BCF of 120.3 L/kg (0.1 µg/L) and 204.6 L/kg (1 µg/L) were reported. During the depuration phase the half-life time for the test substance in fish was 0.9 days (0.1 µg/L) and 1.4 days (1 µg/L). Approximately 90 % of the steady state-concentration of the test substance was excreted after 3.1 days (0.1 µg/L) and 4.8 days (1 µg/L). The lipid content in the study was in the range between 3.01 and 4.62% over the whole uptake and elimination period. Llipid and

growth corrected BCFs were 360 L/kg for the higher exposure concentration (1 µg/L) and 230 for the lower exposure concentration (0.1 µg/L).

The result of the above study is supported by a screening study according to OECD TG 305. The zebrafish (*Danio rerio)* were exposed to a single nominal concentration (1 µg/L) of the ^{14}C-radiolabelled test substance for 21 days in a flow-through system, followed by a 7-days depuration period and the time to steady state was approximately 1 day. A steady-state BCF of 193.44 L/kg and kinetic BCF of 225.6 L/kg was reported. During the depuration phase the half-life of the test substance in fish was 1.17 days (DT90 = 3.9 days).

The DS considered hexyl 2-(1-(diethylaminohydroxyphenyl)methanoyl)benzoate; hexyl 2-[4-(diethylamino)-2-hydroxybenzoyl]benzoate as a substance with low potential to bioaccumulate in aquatic organisms.

Aquatic toxicity

Aquatic toxicity data are available for all three trophic levels, and a summary of the relevant information is provided in the following Table (the key endpoints used in hazard classification are highlighted in bold). hexyl 2-(1-(diethylaminohydroxyphenyl)methanoyl)benzoate; hexyl 2-[4-(diethylamino)-2-hydroxybenzoyl]benzoate has been shown to be poorly water soluble (16 µg/L at 20°C).

Table*: Summary of relevant information on aquatic toxicity*

Method/Exposure	Test organism	Endpoint	Toxicity values in mg a.s./L	Reference/Remarks (reliability refers to Klimisch scores)
Short-term toxicity				
OECD TG 203 Static	*Danio rerio*	96-h LC_{50}	>100 nom	(BASF, 2000b) Rel. 2
OECD TG 202 Static	*Daphnia magna*	48-h EC_{50}	>100 nom	(BASF, 2000a) Rel. 2
OECD TG 201 Static	*Desmodesmus subspicatus*	72-h E_rC_{50}	>100 nom	(BASF, 2001a) Rel. 2
Long-term toxicity				
OECD TG 210 Flow through	*Pimephales promelas*	36-d NOEC	>0.0088 mm	(BASF, 2013) Rel. 1
OECD TG 211 Flow through	*Daphnia magna*	21-d NOEC	⩾0.0142 mm	(BASF, 2009) Rel. 1
OECD TG 211 Semi-static	*Daphnia magna*	21-d NOEC	**0.0001** mm	(BASF, 2007)* Rel. 1 (DS), Rel.3 (REACH registrant)
OECD TG 201 Static	*Desmodesmus subspicatus*	72-h NOE_rC	>100 nom	(BASF, 2001a) Rel. 2
*Study is considered reliable by DS but unreliable by REACH registrant. mm = mean measured; nom = nominal;				

Acute toxicity

Acute aquatic toxicity data are available for fish, invertebrates and algae. The DS proposed not to classify hexyl 2-(1-(diethylaminohydroxyphenyl)methanoyl)benzoate; hexyl 2-[4-(diethylamino)-2-hydroxybenzoyl]benzoate as acutely hazardous to the aquatic environment on the basis that the short-term (acute) aquatic ecotoxicity test results showed no toxic effects to aquatic organisms (algae, daphnia and fish) at concentrations up to the water solubility limit.

Chronic toxicity

Long-term aquatic toxicity data are available for fish, invertebrates and algae.

The limit test on early life-stage toxicity of the test substance to embryos, larvae and young fish was examined according to OECD TG 210 with the fish *Pimephales promelas* in a flow through test system set-up (BASF, 2013). No chronic toxicity to fish was observed up to the limit of water solubility under test conditions (8.8 µg/L).

Two chronic toxicity studies with *Daphnia magna* preformed according to OECD TG 211 were reported by the DS. In the first study (BASF, 2007) the 21 days NOEC based on reproduction was 0.0001 mg/L (mean measured) or 0.001 mg/L (nominal). The study was considered valid by the DS but unreliable by the REACH Registrant, as some validity criteria with respect to shortcomings in the test performance (solvent control, test media) were not (see public consultation). In the second study (limit test) no chronic toxicity to *Daphnia magna* was observed up the limit of water solubility (14.2 µg/L) (BASF, 2009).

A static algal toxicity test according to OECD TG 201 was performed on *Desmodesmus subspicatus* (BASF, 2001a). The test substance showed no toxicity to algae within 72 hours up to the limit of water solubility.

The chronic aquatic classification proposed by the DS (Aquatic Chronic 1, M=1000) was based on the, in their opinion reliable, BASF (2007) chronic toxicity study on *Daphnia magna*.

Comments received during public consultation

Four Member State Competent Authorities (MSCAs) and one company-manufacturer submitted comments during public consultation. One MSCA supported no classification for aquatic acute hazards. Three commenting MSCAs supported the DS proposal to modify the classification to Aquatic Chronic 1, M-factor=1000, while one MSCA did not express a view in relation to the chronic classification.

One MSCA in the first comment pointed out that the substance has a low water solubility (0.01 mg/L) and with a log Koc of 5.1 one might would expect adsorption to organic matter. However, this MSCA agreed with the DS that it cannot be excluded that the observed effects in the BASF 2007 study were due to exposure because no physical effects on the test organisms by non-dissolved test material were reported in the study. In the following targeted public consultation, the DS came to the conclusion that it is possible that the effects occurred due to the particles (physical effect).

The second comment refered to the use of historical control data by the REACH Registrant in the BASF 2007. The MSCA agreed with DS that test results should be compared to the control data of the study because the same study conditions are applied for control and test concentrations. According to OECD TG 211, data from treated animals should be compared with concurrent study control data. RAC agrees with the DS and the commenting MSCA.

The same MSCA considered both chronic studies on invertebrates (BASF, 2007 and BASF, 2009) valid.

A second commenting MSCA required further data to determine the NOEC reliability in the key study (BASF, 2007) and further information regarding QSAR predictions that is available in the REACH registration dossier, available at the ECHA dissemination website.

The company-manufacturer disagreed with the DS proposal to modify the classification to Aquatic Chronic 1, M-factor=1000. The company was of the opinion that the DS proposal is based on a misinterpretation of a chronic daphnia toxicity study (BASF, 2007), which is considered invalid according to the OECD TG 211 by the company due to shortcomings in the test performance (no adequate solvent control used and nutrition composition of the M4 media of control group differed from the treatment groups). The company submitted along with the comments also two expert statements (Galloway, 2017; IBACON, 2017) providing further argumentation regarding the invalidity of the study together with a justification for no classification for chronic aquatic hazards. The ECHA Secretariat has also received a position paper from a Brussels Law Firm (sent on behalf of their client) to which the DS provided his response.

- No adequate solvent control used in BASF 2007 study

Regarding the missing of adequate (solvent) control in the BASF 2007 study the DS agreed with the company that according to OECD TG 211 a solvent control has to be used, when a solvent is used for the preparation of the test concentrations. The DS pointed out that in both studies, BASF 2007 and BASF 2009, the solvent (acetone) was completely evaporated before the test media was added. Therefore, it is not expected that any solvent was present in the medium during the test. Consequently, the available control group is considered an adequate reference to be compared with the treatment groups and the absence of a solvent control does not render the study unreliable. RAC agrees with the explanation and response provided by the DS.

- Differences in the preparation of the test media led to differences in the nutrition composition of the M4-control group compared to the treatment groups.

In the second amendment to the study report it is stated that *"after 2 to 3 days of stirring, precipitation was observed either floating on the surface or being stuck to the magnetic stirrer. This observation only occurred in the test concentrations and not in the control. The precipitation was not determined analytically, but identified by the laboratory assistant as iron. Therefore, it can be concluded that the test media composition was different for the daphnia of the test concentration compared to the test medium for the control group."* The DS pointed out that this observation was not described in the initial study report. Furthermore, in the expert statement by Galloway (2017) it is described that precipitation of iron was noted in the raw data report. RAC notes that the reported deviations regarding test media (precipitation of iron) are not consistent. Regarding the precipitation of iron, the DS is of the opinion that due to the fact that no analytical proof for this hypothesis was provided, this remains speculative. In DS view the reported precipitation, together with the hypothesis of the nature of the precipitate and the contradictions in the reporting are not sufficient to raise reasonable doubt about the results of the study and to consider it unreliable. RAC has no reliable information regarding the identity of the precipitate in test media. RAC is of the opinion that due to the lack of an analysis report demonstrating the presence of the iron in the test media, such a statement cannot be considered scientifically valid.

In the expert statement provided by Galloway (2017), it is stated that variations in metal concentration, including iron, can affect growth and reproduction in daphnia species (Biesinger and Christensen, 1972, Bosnir et al., 2013, Hudson et al., 2016). The DS provided an assessment of the cited publications during the second public consultation (see next section).

QSAR calculations using ECOSAR v1.00 were provided during consultation (BASF, 2018). The resulting values and explanation of the results are provided in the following Table.

***Table**: Results of the QSAR calculations*

Chronic fish toxicity		
Esters	chronic value (33 d) = 4 µg/L	There is an apparent chronic toxicity towards fish within the limit of water solubility (16 ± 3 µg/L).
Phenols	chronic value (30 d) = 8 µg/L	
Neutral organic SAR	chronic value = 4 µg/L	
Chronic daphnia toxicity		
Esters	chronic value (21 d) = 31 µg/L	No chronic toxicity towards daphnia within the limit of water solubility (16±3 µg/L).
Phenols	chronic value (21 d) = 10 µg/L	There is an apparent toxicity within the limit of water solubility.
Neutral organic SAR	chronic value = 9 µg/L	
Note: RAC considers that the QSAR predictions as presented by the company are not well documented and justified (*i.e.* no detailed assessment of applicability domain and reliability).		

After the end of the public consultation (in September 2018), new data was provided including additional experimental studies on different daphnia strains, as well as analytical investigations to identify the nature of the precipitate observed in the BASF 2007 study. This was approached by repeating the preparation of the test media according to the BASF 2007 study protocol and subsequent identification of the precipitate with appropriate analytical methods. More specifically, new *Daphnia magna* reproduction tests (OECD TG 211) performed with M4 medium with and without Fe (II), two new *Daphnia magna* reproduction tests (OECD TG 211) on different strains (including the same one as in the BASF 2007 study) and an investigation of the solubility of the test substances in M4 medium have been provided.

As a result, a second public consultation was launched on the above new information, with three MSCAs and one company-manufacturer submittinged comments..

One MSCA (the DS) provided an assessment of the additional data submitted.

Based on all available information, another MSCA considered that there are uncertainties regarding the BASF (2007) chronic toxicity to *Daphnia magna* study endpoints which impact the study reliability. The same MSCA agreed that the three valid chronic toxicity to *Daphnia magna* studies demonstrate no effects to the limit of solubility in test media.

A summary of the new information and studies submitted by Industry (June 2018) is presented in the Background document.

Assessment and comparison with the classification criteria

Degradation

In the absence of supporting information to justify the QSAR prediction of hydrolysis, no conclusion about the hydrolysis half-life can be drawn by RAC. The substance showed 2-5 % degradation after 28 days in the ready biodegradation test (OECD TG 310 F) and is, thus, considered to be not readily biodegradable. RAC notes that the ready biodegradation study was performed using a test substance concentration that is more than four orders of magnitude above the water solubility limit, so dissolution kinetics may be one reason for limited degradation in this study. Based on available data, RAC agrees with the DS's conclusion that available degradation information does not indicate that it is ultimately degraded (>70%) within 28 days (equivalent to

a degradation half-life of <16 days). Consequently, it is considered to be not rapidly degradable for the purposes of classification under the CLP Regulation.

Bioaccumulation

RAC agrees with the DS that hexyl 2-(1-(diethylaminohydroxyphenyl)methanoyl)benzoate; hexyl 2-[4-(diethylamino)-2-hydroxybenzoyl]benzoate has a low potential to bioaccumulate in aquatic organisms. The basis for this is that the measured BCF value of 360 L/kg (lipid and growth corrected) is below the decisive CLP Regulation criterion of 500.

Acute toxicity

Aquatic acute toxicity data on hexyl 2-(1-(diethylaminohydroxyphenyl)methanoyl)benzoate; hexyl 2-[4-(diethylamino)-2-hydroxybenzoyl]benzoate are available for fish, invertebrates and algae. No effects on aquatic organisms were observed up to the water solubility limit. RAC supports the DS´s proposal that **no classification for acute aquatic hazards is warranted**.

Chronic toxicity

RAC assessed the two new *Daphnia magna* reproduction tests (BASF 2018a and BASF 2018b) and considers them valid and reliable, thus, these studies should be used for classification purposes. In the view of RAC, three reliable chronic toxicity studies on invertebrate *Daphnia magna* are relevant for classification, namely BASF 2009, 2018a and 2018b. RAC considers that the weight of evidence from the by now large body of chronic aquatic data for this substance, shows that there is no chronic aquatic toxicity within the limit of its solubility in water.

21 days Daphnia magna reproduction study (BASF, 2007)

Regarding the identity of precipitate in test media, there is no contemporaneous analysis report. However, the precipitate was identified by the laboratory assistant as iron, based on its colour (brownish) and the fact that it was associated with the magnetic stirrer in the test beaker; it was thus considered to be iron(III)oxide. Additional analytical investigations at a much later date showed that stirring of the M4 medium reduces its iron content and thus impacts the final medium composition used for the *Daphnia magna* reproduction test. This means that control and treatment groups within the BASF (2007) study could have had different nutrient compositions since all test solutions were stirred for 2 to 3 days (but not the control). Iron deficiency in the M4 medium has a negative impact on the reproduction behaviour of daphnids. Fe is essential for Daphnia in haemoglobin synthesis and reproduction (Dave, 1984). Hudson *et al*. (2016) study showed a reduced (but non-significant) maturation rate in Daphnia fed reduced Fe diets. Results of the BASF (2018c) study showed that the absence of soluble iron (Fe(II) from the M4 medium) affect the reproduction of *Daphnia magna* in form of delayed deposition of the brood. A similar delay on the average day of brood deposition was observed in the BASF (2007) study. Therefore the results of the BASF (2007) study are considered by RAC not to be reliable.

Conclusion

RAC is of the opinion that adequate chronic toxicity data are available for all three trophic levels (fish, daphnia and algae). The available information shows no adverse effects to aquatic organisms at concentrations up to the water solubility limit in all reliable tests.

Because the substance is not rapidly degradable, not bioaccumulating and has a chronic toxicity with NOECs above water solubility or hreater than 1 mg/L, RAC is of the opinion that **no classification for chronic aquatic toxicity is warranted**.

Additional references

BASF 2018 BASF Comments on the CHL report by Federal Institute of Occupational Safety and Health (BAuA) on hexyl 2-(1-(diethylaminohydroxyphenyl)methanoyl)benzoate; hexyl 2-[4-(diethylamino)-2-hydroxybenzoyl]benzoate, EC Number: 443-860-6, CAS Number: 302776-68-7, Index Number: 607-693-00-4.

BASF 2018a, Diethylamino Hydroxybenzoyl Hexyl Benzoate using *Daphnia magna* clone M10 (ECT Ökotoxikologie): BASF SE (2018), Report *Daphnia magna* reproduction test, unpublished data, report no. 51E0636/02E020.

BASF 2018b, Diethylamino Hydroxybenzoyl Hexyl Benzoate using *Daphnia magna* clone 5 (IBACON): BASF SE (2018) Report *Daphnia magna* reproduction test, unpublished data,report no. 51E0636/02E019.

BASF 2018c: Report Effects of the absence of soluble iron, Fe(II) in standard M4-Medium on the reproduction of the water flea *Daphnia magna* STRAUS 1820 (Screening Test), unpublished data, report no. 51E0000/18E006.

BASF SE (2009), Report Bestimmung der Wasserlöslichkeit in M4 Medium und in Milli-Q-Water, unpublished data, report no. 08E03159.

Biesinger K and Christensen G., 1972. Effects of various metals on survival, growth, reproduction and metabolism of Daphnia magna. Journal of the Fisheries Research Board of Canada, 29:1691-1700.

Bosnir, J., Puntarić, D., Cvetković, Z., Pollak, L., Barusić, L., Klarić, I., Miskulin, M., Puntarić, I., Puntarić, E., Milosević, M., 2013. Effects of magnesium, chromium, iron and zinc from food supplements on selected aquatic organisms. Collegium Antropologicum 37:965-971.

Dave, G., 1984. Effects on waterborne iron on growth, reproduction, survival and haemoglobin in Daphnia mgna. Comparative. Biochemistry and Physiology, 78C: 433-438.

Hudsona, S.L., Dokeb, D.A., Gohlkea, J.M, 2016. The effect of a low iron diet and early life methylmercury exposure in Daphnia pule. Food Chem Toxicol, 89: 112–119.

Diethylamino Hydroxybenzoyl Hexyl Benzoate, CAS 302776-68-7: Declaration on additional

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).

Annex 3 Records of the targeted public consultation following submission of additional experimental aquatic toxicity studies.