EUROPEAN CHEMICALS AGENCY

Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling at EU level of

Nonylphenol, branched and linear, ethoxylated (with 352 g/mol ≤ average molecular weight < 704 g/mol) [includes ortho-, meta-, para- isomers or any combination thereof]

EC Number: 230-770-5; 248-743-1; 247-555-7; 248-293-6 and others

CAS Number: 127087-87-0; 9016-45-9; 7311-27-5; 27942-27-4; 26264-02-8; 27177-05-5; 14409-72-4 and others

CLH-O-0000007026-79-01/F

Adopted

16 September 2021

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CLH-O-0000007026-79-01/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:	**Nonylphenol, branched and linear, ethoxylated (with 352 g/mol ≤ average molecular weight < 704 g/mol)**
EC Number:	**230-770-5; 248-743-1; 247-555-7; 248-293-6 and others**
CAS Number:	**127087-87-0; 9016-45-9; 7311-27-5; 27942-27-4; 26264-02-8; 27177-05-5; 14409-72-4 and others**

The proposal was submitted by **The Netherlands** and received by RAC on **26 June 2020.**

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

PROCESS FOR ADOPTION OF THE OPINION

The Netherlands 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 **3 August 2020**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **2 October 2020**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Laure Geoffroy**

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 **16 September 2021** by **consensus**.

v

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	Nonylphenol, branched and linear, ethoxylated (with 352 g/mol ≤ average molecular weight < 704 g/mol) [includes ortho-, meta-, para- isomers or any combination thereof]	230-770-5; 248-743-1; 247-555-7; 248-293-6 and others	127087-87-0; 9016-45-9; 7311-27-5; 27942-27-4; 26264-02-8; 27177-05-5; 14409-72-4 and others	Aquatic Chronic 2	H411	GHS09	H411			
RAC opinion	TBD	Nonylphenol, branched and linear, ethoxylated (with 352 g/mol ≤ average molecular weight < 704 g/mol) [includes ortho-, meta-, para- isomers or any combination thereof]	230-770-5; 248-743-1; 247-555-7; 248-293-6 and others	127087-87-0; 9016-45-9; 7311-27-5; 27942-27-4; 26264-02-8; 27177-05-5; 14409-72-4 and others	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410		M=1 M=10	
Resulting Annex VI entry if agreed by COM	TBD	Nonylphenol, branched and linear, ethoxylated (with 352 g/mol ≤ average molecular weight < 704 g/mol) [includes ortho-, meta-, para- isomers or any combination thereof]	230-770-5; 248-743-1; 247-555-7; 248-293-6 and others	127087-87-0; 9016-45-9; 7311-27-5; 27942-27-4; 26264-02-8; 27177-05-5; 14409-72-4 and others	Aquatic Acute 1 Aquatic Chronic 1	H400 H410	GHS09 Wng	H410		M=1 M=10	

GROUNDS FOR ADOPTION OF THE OPINION

ENVIRONMENTAL HAZARD EVALUATION

RAC general comments

Nonylphenols ethoxylated (**NPEs**) are C9 alkylphenols with an ethoxylate chain of variable length and number of repeating units. NPEs have a broad range of uses as detergents, emulsifiers and wetting or dispersing agents. Uses in the textile industry are also reported in washing, dyeing and bleaching processes.

Nonylphenol, branched and linear, ethoxylated (with 352 g/mol ≤ average molecular weight < 704 g/mol) [includes ortho-, meta-, para- isomers or any combination thereof] is further referred to in this opinion as **medium-chain NPEs** with from 3 to <11 ethoxylate units. This opinion is one of three related opinions, the other two concern short-chain (1 to <3) and long chain (11-30) NPEs. The NPEs were divided into these 3 groups based on their aquatic toxicity since the aquatic toxicity is expected to decrease with the increase of the number of ethoxylate groups in the view of the DS.

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Regarding the available reliable data, the DS proposed to classify **medium-chain NPEs** as Aquatic Chronic 2, H411.

With a surface tension lower than 60 mN/m, medium-chain NPEs are surface active, affecting the measurements of different properties such as water solubility and octanol-water partitioning. For the NPE-10.5, water solubility ranging from 37-61 mg/L was determined by the critical micelle concentration.

According to WaterNT estimation, the water solubility of medium-chain NPEs increases with the number of ethoxylated groups. This group has a moderate to strong potential to absorb to organic matter regarding available data for NPE-3, NPE-9, NPE-10 and NPE-10.5. Due to their low vapor pressure and low Henry's law constant, medium-chain NPEs have a low potential for volatilisation.

Rapid Degradability

A summary of the relevant information on rapid degradability is provided by the DS in table 14 of the CLH report.

No data are available for hydrolysis and phototransformation of the medium-chain NPEs.

The DS reported four screening studies considered as valid without restrictions performed with nonylphenol ethoxylate (with n=3, 6, 9.3 and 10). NPE-3 and NPE-10 were shown to reach 52% and 36% mineralization of the test item after 29 and 28 days respectively in a modified Sturm test (OECD TG 301B, GLP compliant). As the pass level for ready biodegradability is 60% of CO_2 emission, NPE-3 and NPE-10 are not considered by the DS as readily biodegradable. In an OECD TG 301A under GLP, NPE-6 and NPE-9.3 reached 63% and 70% removal of DOC after 28 days respectively. The pass level for ready biodegradability of 70% removal of DOC within the 10-d window was not met for both NPEs.

Supportive studies were reported by the DS. NPE-9 reached CO_2 evolution of 69.5% (for unacclimated microbial system) in the ISO 14593 headspace CO_2 biodegradation test (Staples *et al*., 2001) and 75% after 28 days in an OECD TG 301B (Anonymous, 1999). The 10-day window was failed, and the result suggested that NPE-9 incorporated into biomass or adsorbed to suspended material. First order DT_{50} (primary degradation) of 13.6 days was calculated.

The biodegradability of NPE-9.5 was assessed in an OECD TG 301E, not performed under GLP, and monitored by measuring the residual NPE-9.5. This study reported biodegradation at 99% within 8 days at 5 mg/L, 98% within 13 days at 25 g/L and 95% within 14 days at 50 mg/L. The DS explained that the biodegradation rate might be overestimated due to the lack of different controls as the abiotic one.

Three simulation studies in surface water were available for medium-chain NPEs. The studies are reliable with a reliability score of 2 assigned by the DS. A static die-away test was conducted with nonylphenol ethoxylate with an average NPE-8 (NPE-15, NPE-16 and NPE-17 were present in this mixture) and lake water (Mann and Boddy, 2000). After 7-9 days lag phase, almost 100% degradation of NPE-8 was observed after 19 days and 33 days at 22°C under dark and light conditions respectively.

In Jonkers *et al*. (2001), aerobic biodegradation of NPE (NPE-4, NPE-10) was investigated in a laboratory-scale bioreactor filled with river water. 99% of the NPE mixtures were dissipated (primary degradation) after 4 days. Nonylphenol carboxylates (NPECs) were identified as the main group of metabolites.

Biodegradation kinetics of NPEs (n=1-18) was assessed in estuarine conditions by using autochthonous mixed bacterial cultures (Kvestak and Ahel, 1995) during 20 days in the dark for a temperature range from 13°C to 22.5°C. All higher oligomers (NPE > 5) were virtually removed from the solution (after 8 days 100% for NPE-7 to NPE 16 and 95% for NPE-6) and in the later phase of the experiments, concentrations of the most lipophilic oligomers (NPE < 4) increased. These lower oligomers were therefore considered metabolic products of longer chain NPEs (NPE > 4). Biodegradation half-lives ranged from 2.5 to 25 days at 20°C, from 10 to 35 days at 18°C and increased from 23 – 69 days at 13°C.

The DS reported additional information from literature references regarding simulation studies with river water. 87-97% of the initial [^{14}C] 4-NPE-9 was degraded to metabolites other than 4-NP, NPE and NPEC after 128 days (Naylor et al., 2006). Only 0.4% 4-NP was detected (non-labelled test system), suggesting that NP is a minor metabolite under aerobic conditions in river water. After 128 days 40.5% of [^{14}C] 4-NPE-9 converted to $^{14}CO_2$ after an acclimation period of 28 days. Maki *et al*. (1996) conducted river water die-away tests using NPE-9.5 and reported that the predominant metabolite was NPEC1, with minor amounts of NPE2 and NPEC2.

The DS quoted as additional information on NPE-n biodegradation in sediment and soil.

The Dossier Submitter concluded that medium-chain NPEs (n= 3 to < 11) could be considered as not rapidly degradable according to the results of the valid and available biodegradation screening tests. However, the DS noticed that significant levels of biodegradation (52 – 99%) are observed for all NPEs tested indicating they metabolise to some extent. This rate of degradation seems to rise as the number of ethoxylation groups increases. The results of simulation tests with surfaces waters show rapid removal of NPEs and the formation of the more lipophilic short chain NPEs ≤ 2 as degradation products. NPE-1 and NPE-2 are expected to degrade the slowest (Van Vlaardingen *et al.*, 2003) and several studies show that in solution NPE-1/NPE-2 ethoxylates compounds degrade overtime to nonylphenol (European Chemical Agency, 2013; Metcalfe *et al.*, 2001). Moreover, the dossier submitter has prepared a classification dossier where NPE-1 and NPE-2 are also considered not rapidly degradable.

Bioaccumulation

The DS reported a log K_{ow} value of 4.48 (geometric mean) estimated for NPE-3 by Van Vlaardingen *et al*., (2003). Based on KowWIN, log K_{ow} values were obtained for NPE-3 (4.73 and 5.03), NPE-6 (3.91 and 4.20), NPE-7 (3.64 and 3.93) and NPE-10 (2.81 and 3.11).

In the CLH report, a study to determine the n-octanol water partition coefficient (log K_{ow}) for NPE-3 (Ahel and Giger, 1993), using the shake flask method and a normal-phase HPLC, according to OECD TG 107, was described but this method is not suitable for surface active substances.

An accumulation study was performed by Granmo *et al*. (1991) with caged mussels (*Mytilus edulis*) in the unpolluted waters of a fjord on the West Coast of Sweden. The authors of the REACH registration dossier assign this study with a Klimisch score of 2. Nevertheless, the DS considered that the overall quality and reliability of the reported BCF values could not be ascertained because essential information is missing in the study summary and assigned a Klimisch score of 4.

A Klimisch score of 4, instead of 2, was also assigned by the DS to the Keith *at al*. (2001) study. In this study the bioaccumulation potential of NP, NPE-1, NPE-2, and NPE-3 were determined in tissues of fish inhabiting various water bodies.

The DS concluded that in the absence of experimentally and reliable derived BCF values for fish and invertebrates for medium-chain NPEs, experimental and predicted Log K_{ow} data had to be considered for classification purpose.

In the absence of more reliable data, experimental and predicted log K_{ow} data are considered for classification. Experimental and predicted log K_{ow} values for NPE-3 are above 4, the lower end of the group and predicted values for NPE-7 and NPE-10 are below 4, the upper end of the group. The log K_{ow} values for the linear and branched forms for NPE-6 were not in line with each other. The log K_{ow} values for the linear and branched forms were, 4.20 and 3.91 respectively. Considering, that the threshold limit of the group seems to lie at about NPE-6, the DS considered that a definite conclusion on the bioaccumulation potential of NPEs as a group is not considered possible, since the log K_{ow} values fall above and below the CLP trigger of 4.

Aquatic acute toxicity

A summary of the relevant information on aquatic acute toxicity is presented by the DS in table 18 in the CLH report.

For acute aquatic toxicity studies are presented for the three trophic levels, fish, invertebrates, and algae.

For fish, two studies are considered as valid by the DS (Macek and Krzeminski, 1975; Dorn et al., 1993). Bluegill sunfish (*Lepomis macrochirus*) were exposed to NPE-4, NPE-5, NPE-9 and NPE-9.5 under static conditions. The 96h-LC_{50} values for NPE-4, NPE-5, NPE-9 and NPE-9.5 were 1.3, 2.4, 7.9, 7.6 mg/L, respectively. An acute test with fathead minnow (*Pimephales promelas*) was performed in 96-h static renewal exposures, with daily solution replacement using five concentrations of surfactant NPE-9 and a control. Under the test conditions, the 96h-LC_{50} for fathead minnows exposed to NPE-9 was determined to be 4.6 mg/L.

For invertebrates, the DS considered only one Daphnid study as valid. Dorn et al (1993) conducted an acute test using *Daphnia magna* (Strauss) exposed to NPE-9 for 48h in semi-static conditions The EC_{50} for water flea was determined to be 14 mg/L after 48 h exposure to NPE-9.

For the primary producers, two studies performed with the green algae, *Scenedesmus subpicatus*, were considered valid by the DS. The toxicities of NPE-3 and NPE-6 to green alga were determined under GLP using OECD test guideline 201 (Anonymous, 1994a; Anonymous, 1994b). For NPE-3, the EC_{50} for growth rate reduction (ErC_{50}: 0-72h) was 2.9 mg/L; 72h-E_rC_{10} = 1.4 mg/L; 72h-E_bC_{50}

= 2.9 mg/L; 72h-NOE_bC = 1 mg/L. For NPE-6 the 72h EC_{50} for growth rate reduction was 13 mg/L; 72h-E_rC_{10} = 6.1 mg/L; 72h-E_bC_{50} = 3.7 mg/L; 72h-NOE_bC = 3 mg/L.

The DS concluded that as all the endpoints of these valid studies were higher than 1 mg/L, the threshold value for acute aquatic classification purpose according to table 4.1.0(a) of the CLP regulation, the group NPE-n (n= 3 to < 11) is not classified for aquatic acute toxicity.

Aquatic chronic toxicity

The available valid data on chronic aquatic toxicity described by the DS are presented in table 22 of the CLH report.

For chronic aquatic toxicity, studies are presented for fish, invertebrates, and algae.

For fish, a study was conducted to assess the effects of NPE-4 and NPE-9 on growth and survival of the Japanese medaka (*Orizias latipes*) (Balch and Metcalfe, 2006). Exposure to the fry began within 1 day of hatching and continued for 100 days under static conditions. Endpoints reported were secondary sex characteristics, total body length and weight, and development of gonadal intersex (testis-ova). Concentrations of the test compounds declined over the period between test solution renewal. The average measured exposure concentrations determined to be 3.8, 11.4, 38, 114, and 380 µg/L for NPE-4 of 10, 30, 100, 300, and 1000 µg/L; 16.2, 54, 162, and 540 µg/L for NPE-9 of 30, 100, 300, and 1000 µg/L. Fish survival during the 100-day exposure period was greater than 70% in all treatments, except those tested at 380 µg/L of NPE-4. Survival was only 20% in 380 µg/L of NPE-4. The NOEC values for survival are 114 µg/L for NPE-4 and 540 µg/L, the upper concentration for NPE-9.

For invertebrates, the DS reported a valid study performed with water fleas (*Daphnia magna*) and NPE-9 (Dorn *et al*., 1993) following EPA guidelines for estimating the chronic toxicity to aquatic organisms. The reported 7d-LC_{50} for *Daphnia magna* was determined to be 9 mg/L. The NOECs for mortality and for growth were 10 and >10 mg/L.

For the primary producers, the same studies performed with the green algae, *Scenedesmus subpicatus*, and already quoted in aquatic acute toxicity section, were considered valid by the DS (Anonymous, 1994a; Anonymous, 1994b). For NPE-3, 72h E_rC_{10} was 1.4 mg/L and 72h NOE_bC = 1 mg/L. For NPE-6 the 72h E_rC_{10} was 6.1 mg/L and 72h NOE_bC was 3 mg/L.

Since chronic aquatic toxicity information is available for all three trophic levels and as the lowest long-term toxicity values for fish, aquatic invertebrates and algae are 0.114, 10, and 1.4 mg/l, respectively. The DS considered, based on the Japanese medaka 100-day NOEC value of 0.114 mg/L, and according to Table 4.1.0 (b)(i) for non-rapidly degradable substances, medium-chain NPEs (n=3 to <11) fulfils the criteria for classification as Aquatic Chronic category 2, H411.

Comments received during consultation

During the consultation, one MSCA and one other national authority commented on the classification proposals of the Dossier Submitter. Both support the classification proposal for medium-chain NPEs as Aquatic Chronic 2. Nevertheless, the national authority asked to clarify the basis of this classification regarding the use of a 100-day NOEC of 0.114 mg/L for the survival of *O. latipes* exposed to NPE-4 (Balch and Metcalfe, 2006). Indeed, the recent 2018 Substance Evaluation (SEv) for nonylphenol, branched, ethoxylated (EC 500-315-8, CAS 127087-87-0) and the REACH registration dossier for nonylphenol, branched, ethoxylated (1 - 2.5 moles ethoxylated, CAS 68412-54-4, EC 500-209-1) considered that there were no effects on survival in the study with NPE-4 at any concentration, leading to a 100d NOEC of = ≥0.380 mg/L (mm).

The national authority noticed that since all other aquatic chronic toxicity values that are considered valid by the DS for the CLH report are above 1 mg/L, it would not result in a classification for aquatic chronic toxicity given that the substance is NRD. However, the surrogate approach would be applicable using the LC_{50} values for *L. macrochirus* and *P. promelas* since there are no reliable chronic toxicity data for these fish species. These LC_{50} values are in the range of >1 to ≤10 mg/L, leading to an Aquatic Chronic 2 classification.

The DS reviewed the original study report to clarify these inconsistencies (Balch and Metcalfe, 2006) and confirmed that during the 100-day exposure period, fish survival was greater than 70% in all treatments, excluding those tested at 1000 µg/L of NPE-4. Survival was only 20% in the 1000 µg/L NPE-4. Therefore, effects on survival at the highest concentration of NPE-4 were observed and the DS considered that the 100-day NOEC of 0.114 mg/L based on survival should be used for classification purposes.

Assessment and comparison with the classification criteria

Degradation

No data are available for hydrolysis and photo-transformation of the medium-chain NPEs but as the chemical structure is stable and the ethoxylated chain is not suspected to be degraded via hydrolysis, it is assumed that abiotic processes are not relevant degradation processes for medium-chain NPEs.

According to the CLP regulation, a substance is considered to be not rapidly degradable unless at least one of the following is fulfilled:

a. The substance is demonstrated to be readily biodegradable in a 28-day test for ready biodegradability. The pass level of the test (70% DOC removal or 60% theoretical oxygen demand) must be achieved within 10 days from the onset of biodegradation, if it is possible to evaluate this according to the available test data (the ten-day window condition may be waived for complex multi-component substances and the pass level applied at 28 days, as discussed in II.2.3). If this is not possible, then the pass level should be evaluated within a 14-day window if possible, or after the end of the test; or
b. The substance is demonstrated to be ultimately degraded in a surface water simulation test with a half-life of < 16 days (corresponding to a degradation of > 70% within 28 days); or
c. The substance is demonstrated to be primarily degraded biotically or abiotically e.g., via hydrolysis, in the aquatic environment with a half-life < 16 days (corresponding to a degradation of > 70% within 28 days), and it can be demonstrated that the degradation products do not fulfil the criteria for classification as hazardous to the aquatic environment.

RAC notes that ready biodegradability results from the standard screening test methods show that medium-chain NPEs are not readily biodegradable (e.g., the application of the 10-day window criterion). However, significant levels of primary degradation (52 – 99%) are observed for all NPEs and in the water simulation studies. Different metabolites were identified and among them, NPECs, NPE-1 and NPE-2. These metabolites are part of the short-chain NPEs, considered as not rapidly degradable and proposed for a harmonised classification as Aquatic Acute 1, with M factor = 1 and Aquatic Chronic 1, with M factor = 10

Overall, RAC considers medium-chain NPEs (n= ≤ 3 to < 11) **as not rapidly degradable** for purposes of classification.

Bioaccumulation

RAC is of the opinion that in the absence of experimentally and reliable derived BCF values for fish and invertebrates for medium-chain NPEs, predicted Log K_{ow} data has to be considered for classification purposes. Nevertheless, RAC noted the uncertainties of these data related to the surface-active property of these substances.

RAC notes that the results of experimental and predicted log K_{ow} values for NPE-3 are above 4 and for NPE-7 and NPE-10 are below 4. The DS estimated that the threshold limit of the group seems to lie at about NPE-6. As the bioaccumulation potential cannot be excluded from this group, RAC proposes to consider that the medium-chain NPEs **have a potential to bioaccumulate** according to CLP criteria.

Aquatic toxicity

RAC understands that medium-chain NPEs degrade in a unique way, primarily through the loss of units from the ethoxylate chain, while the alkyl chain remains relatively stable, particularly if branched. Each EO unit has a slightly negative theoretical log Kow value, so as the EO chain shortens through degradation, the overall log K_{ow} of the NPE increases gradually, as does its aquatic toxicity. Once the EO chain has shortened to 1 to 3 remaining units, it's endocrine properties also become more active. Thus, RAC considers that the environmental degradation of NPEs needs to be taken into account when considering the classification of the medium and long-chain NPEs.

On the issue of degradation products, section 4.1.3.3.1 of the Guidance on the Application of the CLP criteria indicates the following:

> "*There may be occasions, however, when a substance so tested may degrade to give rise to a more hazardous product. In these circumstances, the classification of the parent compound should take due account of the hazard of the degradation product, and the rate at which it can be formed under normal environmental conditions (for detailed information please check also the Annexes to this guidance).*"

In this context, the assessment of the relevance of degradation products for the classification and labelling of the parent substance depends on the relative toxicity of the degradation products, the quantity produced, and the time frame.

RAC notes that the results of simulation tests with surfaces waters show rapid degradation of NPEs and the formation of the more lipophilic short chain NPEs ≤ 2 as degradation products. RAC considers that the high rate of primary degradation to NPEs ≤ 2 indicates that the toxicity of short-chain NPEs must be taken into account when making a classification assessment of long-chain NPEs.

Table 1: *Summary of the available acute and chronic toxicity data compared with the CLP criteria. Key endpoints used in acute and chronic hazard classification are highlighted in bold.*

Method	Substance tested	Results (mg/L)	Remarks	Reference
		Acute toxicity		
Fish				
Test guideline not mentioned Bluegill sunfish (*Lepomis macrochirus*) 96h exposure	**NPE-4 NPE-5 NPE-9 NPE-9.5**	**96h LC_{50} = 1.3 96h LC_{50} = 2.4 96h LC_{50} = 7.9 96h LC_{50} = 7.6 (n)**	**Static RI = 2**	**Macek and Krzeminski (1975)**
Test guideline not	NPE-9	96h LC_{50} = 4.6	Semi-static	Dorn *et al.*

mentioned Fathead minnow *(Pimephales promelas)* 96h exposure		(mm)	RI = 2	(1993)
Invertebrates				
Test guideline not mentioned *Daphnia magna* 48h exposure	NPE-9	48h EC_{50} = 14 mg/L (mm)	Semi-static RI = 2	Dorn *et al.* (1993)
Algae				
According to OECD TG 201 *Scenedesmus subspicatus* 72h exposure	NPE-3 NPE-6	72h E_rC_{50}= 2.9 72h E_rC_{50}=13 (n)	Static; RI = 2	Anonymous (1994ab)
Chronic toxicity				
Fish				
Not a test guideline method 100d exposure Medaka (*Oryzias latipes)*	**NPE-4** **NPE-9**	**NOEC survival =0.114** **NOEC SSC = 0.38** **(mm)** **NOEC survival =0.54** **NOEC SSC = 0.54** **(mm)**	**Static;** **Endpoint: mixed secondary sexual characteristics** **RI = 2**	**Balch and Metcalfe (2006)**
Invertebrates				
EPA guideline *Daphnia magna* 7-d exposure	NPE-9	NOEC mortality = 10 NOEC growth > 10 (m)	Semi-static; RI = 2	Dorn *et al*. (1993)
Algae				
According to OECD TG 201 *Scenedesmus subspicatus* 72h exposure	NPE-3 NPE-6	72h E_rC_{10}= 1.4 72h E_rC_{10}=6.1 (n)	Static; RI = 2	Anonymous (1994b)

VTG = vitellogenin, mm = mean measured concentrations, n = nominal concentrations.

<u>Aquatic acute classification</u>

A full acute dataset (fish, aquatic invertebrates, algae) is available for medium-chain NPEs. Nevertheless, RAC notes that a specific sensitivity of *Mysidopsis bahia* cannot be excluded regarding the tests with a Klimisch Score of 3 or 4 (Patoxzka and Pulliam, 1990; Hall *et al*., 1989) and the classification of the short-chain NPEs group and was not considered in this dataset. RAC agrees with the DS that data for medium-chain NPEs do indeed indicate no classification for acute aquatic hazards as all valid values are > 1 mg/L. However, as RAC considers that the short-chain NPE degradation products are relevant for classification of the medium-chain NPEs, data from these should be compared with the CLP criteria.

As the available short-chain NPEs $L(E)C_{50}$s for fish and aquatic invertebrates are 0.218 mg/L (NPE-1) and 0.328 mg/L (NPE-1), respectively, and as these values are lower than the classification threshold value of 1 mg/L, RAC agrees that medium-chain NPEs (3 to < 11 ethoxylate groups) fulfil the criteria for classification **as Aquatic Acute Category 1, H400**. According to CLP table 4.1.3, a **M-factor=1** is warranted for $L(E)C_{50}$s ranged from 0.1 to 1 mg/L.

Aquatic chronic toxicity

RAC notes that the DS considered that chronic toxicity data are available for the three trophic levels fish, invertebrates, algae. RAC agrees the use of the 100-day NOEC of 0.114 mg/L based on Japanese medaka survival (Balch and Metcalfe, 2006) for classification purpose. Since mortality is observed in the highest concentration tested, this NOEC has not resulted from a concentration limit. This is not the case for the NPE-9 100-day NOEC because the reported value of 0.54 mg/L corresponds to measured value of the 1 mg/L nominal concentration. For NPE-9, no significant adverse effects are observed in this study and the NOEC is totally dependent of the test design. RAC considers this value as not relevant.

RAC notes that a 7-day exposure with *Daphnia magna* is the only valid test for invertebrates (Dorn *et al*., 1993). However, this test was conducted according to EPA guideline recommending the use of *Ceriodaphnia*. Regarding the Daphnia lifespan compared to *Ceriodaphnia*, the parameters reported (survival and growth, no data on reproduction), this test should be considered more as a prolonged exposure instead of a chronic toxicity test. Moreover, reported data should be clarified as the 7d LC_{50} was determined to be 9 mg/L and the NOECs for mortality and growth were 10 and > 10 mg/L. Furthermore, in two studies invalidated by the DS (RI = 4 might be more appropriate), a 7d exposure test with *Ceriodaphnia* and a 5d exposure with *Moina macrocopa*, a 7d EC_{50} of 0.2 mg/L and a NOEC growth and reproduction < 0.021 mg/L were reported respectively.

Overall, RAC concurs with the Dossier Submitter that based on the Japanese medaka 100-day NOEC value of 0.114 mg/L, and according to Table 4.1.0 (b)(i) for non-rapidly degradable substances, medium-chain NPEs (n=3 to <11) fulfils the criteria for classification as Aquatic Chronic category 2, H411. However, as RAC considers that the short-chain NPE degradation products are relevant for classification of the medium-chain NPEs, data from these should be compared with the CLP criteria.

Chronic toxicity data for short-chain NPEs are available for fish, aquatic invertebrates, and algae.

RAC noted that for fish studies, few of them presented results for endpoints normally used for classification purpose as growth and survival. Most results of these studies are related to endocrine disrupting effects. Survival and growth endpoints may not be the most sensitive. For example, from the Medaka studies, a NOEC for reproduction in the range 0.035-0.1 mg/L was suggested by the observed effects on secondary sex characteristics for NPE-1 as proposed in the SEv dossier. RAC considers the most sensitive species to be *M. bahia* with a 28-day NOEC value of 0.0077 mg/L. RAC agrees that as short-chain NPEs are not rapidly degradable substances, medium-chain NPEs (3 to < 11 ethoxylate groups) fulfil the criteria for classification as **Aquatic Chronic 1, H410. An M-factor of 10** is warranted based on the NOEC between 0.001 and 0.01 mg/L.

As degradation products with NPE ≤ 2 are relevant for classification of the parent substance (long-chain NPEs) and require a more stringent classification than data for long-chain NPEs indicates, RAC concludes that long-chain NPEs warrant classification as:

Aquatic Acute 1 (H400), M = 1

Aquatic Chronic 1 (H410), M = 10.

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).