Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

Quinolin-8-ol; 8-hydroxyquinoline

EC Number: 205-711-1
CAS Number: 148-24-3

CLH-O-0000001412-86-60/F

Adopted

05 June 2015

SPECIFICATION
COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that some attachments received may have been copied in the table below. The attachments received have been provided in full to the dossier submitter and RAC.

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Substance name: quinolin-8-ol; 8-hydroxyquinoline
CAS number: 148-24-3
EC number: 205-711-1
Dossier submitter: Spain

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
07.11.2014	France		MemberState	1
Comment received				
FR agrees with the classification proposed for health hazards. France considers also that there is enough information to enable a classification of 8-hydroxyquinoline as STOT SE cat 3 for narcotic effects. FR agrees with the classification and M factors proposed for Environmental hazards. Please, minor modifications are needed in sections 3.1.1. and 3.1.2. (p.15): There is a typo in the substance name (hidroxyquinoline instead of 8-hydroxyquinoline).				
Dossier Submitter's Response				
Regarding the possibility to classify 8-hydroxyquinoline as STOT SE cat 3 for narcotic effects, see response to comment number 11. Based on the Dutch comment received, the Spanish CA has changed the classification regarding toxicity to reproduction (see response to comment number 4 and 5).				
RAC's response				
Noted. Regarding STOT SE see below.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
04.11.2014	Netherlands		MemberState	2
Comment received				
The NL CA agrees for no classification for carcinogenicity because the marginal increases in male rats (C-cell adenomas/carcinomas in the thyroid and alveolar/bronchiolar adenomas or carcinomas combined) were not regarded as being related to the administration of 8-hydroxyquinoline. In addition, these changes were not supported by an increase in epithelial hyperplasia.				
Dossier Submitter's Response				
Thank for agreeing.				
RAC's response				
Noted.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
04.11.2014	Netherlands		MemberState	3
Comment received				
The NL CA agrees for no classification for mutagenicity because all in vivo tests (micronucleus test in peripheral blood and spermatogonial cells) performed according to OECD guidelines were negative. The in vivo micronucleus test by Hamoud et al. 1989 reported a non-reproducible positive result with no positive control, and no purity and batch information. Five out of the six in vivo studies resulted in negative results. 8-Hydroxyquinoline is a proteasome inhibitor which often gives false positive results due to its iron chelating properties which cause DNA strand breaks (Magkoufopoulou et al. 2011).				
Dossier Submitter's Response				
Thank you for your agreement with our proposal on genotoxicity.				
RAC's response				
The statement of the NL CA is in agreement with conclusion of the DS regarding the genotoxicity.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
05.11.2014	Germany	Probelte SA	BehalfOfAnOrganisation	4
Comment received				
We agree with non-classification for reproductive toxicity regarding sexual function and fertility. We disagree with the proposed classification for developmental toxicity based on findings in a rabbit developmental study (Fascineli, 2006): Please refer to the enclosed expert statement Pfau (2014). It is concluded that the observed effect in the rabbit is not relevant to humans. Thus, a classification of 8-Hydroxyquinoline for developmental toxicity is not warranted.				
Dossier Submitter's Response				
A number of chelating agents can interact with metal ions directly by chelation causing trace element deficiencies. It has been demonstrated that the teratogenic potential of chelators such as D-penicillamine is, at least in part, due to these element trace deficiencies. For instance, zinc deficiency during pregnancy is teratogenic as observed in animal models including cleft and lip palate, brain and eye malformations and numerous abnormalities of heart, lungs and urogenital system. To make matters worse, maternal nutritional status is one component that can modulate the expression of many reproductive insults and developmental toxicity could be amplified in women characterized by suboptimal nutritional status. 8-hydroxyquinoline has also chelating properties that could scavenge essential metal ions causing a deficiency in micronutrients that could affect the offspring. Taking into account all the available data, the external malformation omphalocele observed in developmental study rabbits could be a consequence of the chelating activity of the substance on some micronutrients. However, the confirmation of this mechanism would not mean the loss of relevance of omphalocele in humans. Besides, other mechanisms could also be implied. The possible mechanism of chelation of metal ions to induce developmental toxicity would support, in opinion of the Spanish CA, the relevance of this rare abnormality				

(omphalocele) and accordingly the classification of 8-hydroxyquinoline for developmental toxicity.

Therefore, the Spanish CA, after a detailed and careful review of your comment, regards classification for 8-hydroxyquinoline for developmental toxicity warranted.

Furthermore, the Spanish CA has reconsidered its original proposal for C&L and now considers classification as Repr.1B; H360D warranted (see response to comment number 5).

RAC's response

Industry's view and the DS response have been considered.

Date	Country	Organisation	Type of Organisation	Comment number
04.11.2014	Netherlands		MemberState	5

Comment received

The NL CA disagrees with the Repro classification due to the teratogenic effects in rabbits (increase in omphalocele, a rare malformation) at 15 mg/kg bw/day in the presence of maternal toxicity (16% of dams showed nervous system symptoms including excitation followed by lethargy at 15 mg/kg bw/day). Other anomalies were also reported in a developmental and 2-generation rat study in the presence of maternal toxicity. In our opinion Cat 1B should be considered because the teratogenic effects at 15 mg/kg bw/day were observed in animals without maternal toxicity. We do not agree with the current argumentation. The fact that comparable effects were not observed in rats would not warrant a lower classification because developmental studies are performed in two species to increase the sensitivity. This is also in line with CLP Annex I paragraph 3.7.2.2.3 which states that a single positive result may justify classification. The fact that other effects were observed in the presence of maternal toxicity does not allow a conclusion that the increase in omphalocele may also be secondary to maternal toxicity. In addition the lower in live birth rate in the 2-generation study (significant, dose related and outside historical control incidence, both generations) may be considered a developmental effect supporting the classification.

The Netherlands agrees for no classification for fertility and lactation.

Dossier Submitter's Response

In the CLH Report, we proposed to classify this substance as Repro. Cat. 2 for its developmental toxicity based mainly on the occurrence of a rare malformation (omphalocele), in absence of maternal toxicity and with an incidence out of the range of historical control value. However, a reasonable uncertainty between category 1B and 2 based on the available data in rabbits was commented in the CLH proposal "The incidence of omphalocele in rabbit at the mid dose level in absence of maternal toxicity raises a discussion on what category, 1B or 2, is more suitable for classification".

Maternal toxicity in rabbits was manifested at 15 mg/kg bw/day (16% of the dams) by nervous system excitation followed by lethargy after test item administration. However, when individual data for offspring is correlated with their parents, the teratogenic effects were observed in all animals without maternal toxicity.

Besides, it has to be noted that information provided during this public consultation indicates that 8-hydroxyquinoline mechanism of action (MoA) of teratogenicity could be chelation of relevant micronutrients such as metal ions. Several publications have noted that chelators can induce developmental toxicity in humans (Domingo, 1998; NRS, 2000;

Keen, 2003). Developing organism seems to be more susceptible to this MoA and long-term consequences more severe than in the adult. The mother might recover while the offspring could be permanently affected, worsened in cases of offspring from mothers with suboptimal nutritional status.
Even if adverse developmental findings observed in the offspring were due to maternal toxicity in the form of low serum micronutrient concentrations, these effects may be relevant for developmetal classification. According to the Guidance on the Application of the CLP Criteria classification criteria in section 3.7.2.2.1.2 "In cases where a causal relathionship is established between reproductive and parental toxicity and the effects on the offspring can be proved to be secondary to maternal toxicity, they may still be relevant for developmental classification, dependent on the severity of the effects.
A comparison between the severity of the maternal toxicity and the severity of the findings in the offspring must be performed. There are several examples showing that the developing organism can be more susceptible and the long-term consequences can be more severe than in the adult. The mother might recover while the offspring could be permanently affected".

In the comments from NL it is mentioned that the low birth live rate in 2-generation study (significant, dose related and outside historical control incidence, both generations) may be considered a developmental effect supporting the classification as Category 1B. As stated in the CLH proposal this decrease in the birth rate in the 2-generation study in rat occurred at 8000 ppm with clear signs of maternal toxicity manifested by significant decreases of bodyweight, bodyweight gain, food consumption and changes in the weight of organs from the dose level of 3000 ppm. It has to be taken into account that dose level of 8000 ppm (678-933 mg/kg bw/day) corresponds to one close to the LD_{50} obtained in rats (790 mg/kg bw). Accordingly, as previously mentioned in the CLH proposal, the Spanish CA regarded these effects only as supportive evidence of developmental toxicity.

Therefore, based mainly on the occurrence of this rare malformation (omphalocele) with an incidence out of the range of historical control value and considering the possible relevance of the MoA in humans, the Spanish CA agrees to modify its position on the classification category for development to 1B.
The Spanish CA is of the opinion that a cautious view should prevail and 8-hydroxyquinoline should be classified as H360D; Category 1B.

References:

- Domingo, J.L. (1998). J Nutr. 2003 May; 133(5 Suppl 2):1597S-1605S.
- National Research Council (US) Committee on Copper in Drinking Water. Washington (DC): National Academies Press (US); 2000.
- Keen, C.L., Clegg, M.S., L.A. Hanna, L. Lanoue, J.M. Rogers, G.P. Daston, P. Oteiza and J.Y. Uriu-Adams (2012). The Plausibility of Micronutrient Deficiencies Being a Significant Contributing Factor to the Occurrence of Pregnancy Complications. J Nutr. 2003 May; 133(5 Suppl 2):1597S-1605S.

RAC's response

The revised CLH proposal has been considered in the opinion document.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
05.11.2014	Spain	Probelte SA	BehalfOfAnOrganisation	6
Comment received				

Classification for acute oral toxicity is based on a mouse study (Dickhaus & Heisler, 1981b) LD50 177 mg/kg bw) with mortalities occurring within 24h after administration.
Please refer to the enclosed expert statement Pfau (2014).

Considering the weight of evidence the observation of the LD50 in the Dickhaus & Heisler (1981b) study is considered spurious and may be due to impurities in the test item, as no specification or analysis was provided.
A more reasonable but conservative classification is proposed:
Acute Tox 4 H302, Harmful if swallowed

ECHA comment: Please refer to to the following attachments:

1. Comments on the CLH report - Proposal for Harmonised Classification and Labelling, Substance Name: 8-hydroxyquinoline, Version 3, September 2014 – submitted by Probelte SA on 5 November 2014
2. 8-Hydroxyquinoline - Comments on the proposed classification and labelling according to the CLH report – submitted by Probelte SA on 5 November 2014

Dossier Submitter's Response

As mentioned in Probelte comments the test item purity was not specified in the mice acute oral toxicity study (Dickhaus and Heisler, 1981b). However, in the rat acute oral toxicity study (Dickhaus and Heisler, 1981a), the test item purity was not mentioned either. Both studies were accepted during the inclusion of the active substance 8-hydroxyquinoline under Regulation (EC) No 1107/2009 and therefore the Spanish CA is of the opinion that they have to be taken into consideration to assess the acute oral toxicity of the active substance in the absence of more appropriate studies. The proposed classification is based on the LD_{50} of 177 mg/kg bw obtained in the study with CFI mice (Dickhaus and Heisler, 1981b) but it is also supported by the oral LD_{50} values reported in the EMEA document for 8-hydroxiquinilone (EMEA/MRL/464/98-FINAL) in a range of 220 to 280 mg/kg bw for mice.

In Probelte comments it is stated that mortality observed in repeated toxicity studies carried out with mice (NTP, 1985) was lower to that observed in Dickhaus acute oral study. However, as already noted in the CLH proposal, the short term toxicity studies in mice (NTP, 1985) were considered acceptable only as additional information. Besides, they were carried out with B6C3F1 mice and the test substance was administered in the diet, whereas the acute oral toxicity study was performed with CFI mice and the administration was via stomach rigid tube. It has to be pointed out that according to Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 the adequate method of administration in acute oral toxicity studies is "single dose by gavage using a stomach tube or a suitable intubation cannula". Therefore, the Spanish CA is of the opinion that the results in short term toxicity and the acute oral toxicity studies in mice are not comparable.

The comments also mentioned the *in vivo* spermatogonial chromosome aberration study (August, 2007) in which mortality was not observed up to 300 mg/kg bw after oral gavage. However, after a detailed review of this study it has been observed that mortality occurred in the two tested groups treated with 300 mg/kg bw. 1/7 animals in group 4 and 1/7 animals in group 7 of the main study died after dosing at 300 mg/kg bw. Furthermore, the study was performed with NMRI mice, a different strain of mouse to that used in the Dickhaus acute oral study. Therefore, these studies are not comparable.

We consider that classification should be based on the lowest LD_{50} in the most sensitive species and strain used. Consequently, regarding the whole available data about acute oral toxicity, including information from the EMEA document, and in the absence of more

appropriate studies, the MSCA regards not sufficiently cautious to dismiss the LD_{50} of 177 mg/kg bw observed in Dickhaus study with CFI mice. Therefore, we maintain the proposal of classification for 8-hydroxyquinoline as H301, Category 3.
RAC's response
The rapporteur agrees with the DS. The information is considered in the opinion document.

Date	Country	Organisation	Type of Organisation	Comment number
04.11.2014	Netherlands		MemberState	7
Comment received				
The NL CA agrees with the classification for Acute Tox. 3 (H301) because of the reported oral LD50 of 177 mg/kg bw in mice (Cat. 3: Oral LD50 > 50 but ≤ 300 mg/kg bw).				
Dossier Submitter's Response				
Thanks for your agreement. See also response to comment number 6.				
RAC's response				
Considered for the proposal				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
04.11.2014	Netherlands		MemberState	8
Comment received				
The NL CA agrees for no classification for skin irritation.				
Dossier Submitter's Response				
Thanks for agreeing.				
RAC's response				
Noted				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
04.11.2014	Netherlands		MemberState	9
Comment received				
The NL CA agrees with the classification for Eye Dam. 1 (H318) because at least one rabbit had corneal opacity which persisted until day 20 (Table 12, p. 21 CLH Report).				
Dossier Submitter's Response				
Thanks for agreeing.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
04.11.2014	Netherlands		MemberState	10
Comment received				
The NL CA agrees with the proposed Skin Sens. 1 (H317) classification because sensitization in humans studies was reported in 3 studies with a sensitization rate of 4.7, 8 and 6%; all considered high frequency (≥ 0.2% of general population, ≥ 1% of selected dermatitis patients and ≥ 2% selected dermatitis patients). Sub-categorization is not possible due to lack of information with regards to grade of exposure, duration of studies (in some cases) and mode of application.				

Dossier Submitter's Response
Thanks for your agreement.
RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
07.11.2014	France		MemberState	11
Comment received				

4.12.1.1 Neurotoxicity:
France considers that the classification of 8-hydroxyquinoline for its neurotoxic potential should be further discussed.
According the regulation (EC) No 1272/2008, the criteria for classifying substances for specific target organ toxicity-single exposure as Category 3 for narcotic effects are:
(a) central nervous system depression including narcotic effects in humans such as drowsiness, narcosis, reduced alertness, loss of reflexes, lack of coordination, and vertigo are included. These effects can also be manifested as severe headache or nausea, and can lead to reduced judgment, dizziness, irritability, fatigue, impaired memory function, deficits in perception and coordination, reaction time, or sleepiness;
(b) narcotic effects observed in animal studies may include lethargy, lack of coordination, loss of righting reflex, and ataxia.

Based on these criteria, France considers that there is enough information to enable a classification of 8-hydroxyquinoline as STOT SE cat 3 for narcotic effects. Indeed, neurotoxic effects of 8-hydroxyquinoline and halogenated hydroxyquinoline derivates were observed both in animals and in human.

In developmental toxicity studies, transient nervous excitation followed by lethargy after the administration of 8-hydroxyquinoline were observed both in rats and rabbits. In rats, observed effects were noted at dose treatment groups of 300 and 600 mg/kg bw/d (Fascineli, 2006c) and in rabbits at dosed treatment groups of 15 and 60 mg/kg bw/d (Fascineli, 2006d).

In a Wistar rats acute oral study (Dickhaus and Heisler, 1981a), all treated animals (600, 756, 953 and 1200 mg/kg bw) showed ataxia, gasping breathing and disturbed coordination within 1 hour after administration. Sedation (at all dose levels) and coma were noted after that. Although an LD50 of 790 (females) and 800 (males) mg/kg bw was set, the surviving rats also displayed increased nervousness.

In a second CFI mice acute oral study (Dickhaus and Heisler ,1981b), animals dosed at 120, 151, 190 and 240mg/kg bw/d, displayed dose related reduced activity, a decrease in respiratory rate, spasm and diminished reflex response up to 24 hours. An LD50 was set at 177 mg/kg bw (both sexes). During the rest of the follow-up observation period, the surviving mice displayed sedation and reduced reactions.

Furthermore, some symptoms of acute intoxication with 8-Hydroxiquinoline were described in mice during the determination of intraperitoneal LD50. Although the signs were reported at lethal doses (death within 5 to 10 minutes after administration) it should be noted that they included confusion, respiratory difficulty, occasional hind leg paralysis and terminally, violent convulsion. Doses leading to delayed death (later than 6 hours post administration)

result in anorexia, malaise, slow protective reflex action and general indifference to optical and acoustical stimuli. In dog, after a single intravenous dose of 10 mg/kg bw and above, significant central nervous system toxicity, presenting as anxiety or convulsion were noted (EMEA/MRL/464/98-FINAL. July 1998).

These neurotoxic effects observed in animals after administration of 8-hydroxyquinoline are supported by human data on halogenated hydroxyquinoline derivatives, 5-chloro-7-iodo-8-hydroxyquinoline. Indeed, encephalopathy was related to the ingestion of a high dose of clioquinol over a short period. The neurotoxic effect consisted of drowsiness, mental confusion, disorientation, hallucinations, and headache with subsequent amnesia for events during the episode (Baumgartner, G. et al, 1979).

Dossier Submitter's Response

Narcotic effects not to be life-threatening observed after short duration exposure and with a recovery in a reasonable period are those considered **for the STOT SE 3** according to CLP Regulation. It has to be noted that the LD_{50} of 177 mg/kg bw obtained in the acute oral toxicity study in mice (Dickhaus, 1981b) lead to a classification for 8-hydroxyquinoline as Acute Tox. 3; H331 (50 mg/kg bw < LD_{50} < 300 mg/kg bw). According to the ECHA Guidance on the Application of the CLP Criteria (November, 2013), "Care must be taken not to classify for STOT-SE for effects which are not yet lethal at a certain dose, but would lead to lethality within the numeric classification criteria. In other words, if lethality would occur at relevant doses then a classification for acute toxicity would take precedence and STOT-SE would not be assigned". This was stated for STOT SE 1 and 2 but it is also valid for STOT SE 3. Data mentioned in the comment about acute oral toxicity studies in mice and rat (Dickhaus, 1981a and 1981b) and for the intraperitoneal LD_{50} (EMEA/MRL/464/98-FINAL) should be taken with care since the effects were observed at dose levels close or above the LD_{50} and they can be considered clear signs of toxicity that have the potential to cause lethality. The most appropriate class, acute oral toxicity or STOT SE 3, should be assigned to avoid a double classification. The Spanish CA is of the opinion that signs observed after single exposure are yet covered by the proposed classification for acute oral toxicity.

Effects in developmental studies observed in the absence of lethality were transient signs of nervous system excitation followed by lethargy. However, evaluation of available information on 8-hydroxyquinoline repeated dose toxicity indicates that most of studies showed no effects after test item administration.

Besides, the MSCA regards not suitable to take into consideration data from open literature referred to 8-hydroxyquinoline halogenated derivatives to support a possible classification for STOT SE 3 (narcotic effects). The Spanish CA remarked in the CLH proposal the severe neurotoxic effects observed after ingestion of clioquinol, a halogenated derivative of 8-hydroxyquinoline (Baumgartner, 1979). However, 8-hydroxyquinoline and clioquinol have different chemical structure and therefore we are of the opinion that data from this compound are not conclusive for the hazard assessment of 8-hydroxyquinoine and accordingly for the STOT SE 3 classification (narcotic effects).

Taking into account that most of the observed effects after single exposure are yet covered by the proposed acute oral classification and considering inconclusive the data from halogenated derivatives, the Spanish CA regards the available data not sufficient to classify 8-hydroxyquinoline for STOT SE 3 for narcotic effects.

RAC's response

The information and discussion are reflected in the opinion document.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
04.11.2014	Netherlands		MemberState	12
Comment received				
The NL CA agrees with no classification for repeated dose toxicity. References: Magkoufopoulou, C., Claessen, S.M., Jennen, G.G., Kleinjans, J.C., and van Delft, J.H. (2011) Comparison of phenotypic and transcriptomic effects of the false positive genotoxins, true genotoxins and non-genotoxins using HepG2 cells. Mutagenesis 26 (5): 593-604. NTP (2014) National Toxicology Program Database search 22 october 2014. http://ntp.niehs.nih.gov/testing/status/agents/ts-10598-n.html				
Dossier Submitter's Response				
Thanks for your support.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
10.11.2014	United Kingdom		MemberState	13
Comment received				
Aquatic toxicity (Section 5.4): The aquatic ecotoxicity endpoints in the CLH Report are derived from the 'Beltanol-L' formulation which is an approximate 50% w/w solution of 8-HQ sulphate. All endpoints were subsequently expressed as measured 8-HQ values rather than as the sulphate. We cannot see in the report a justification for using data on the formulation and sulphate form of the substance rather than on the pure 8-hydroxyquinoline. Isn't the CLH Report actually on 8-hydroxyquinoline sulphate? We note that the pure form may be difficult to test because of solubility issues but a case should be made as to why these data and this hazard assessment also covers 8-hydroxyquinoline. At Section 5.4.1.2 only a 28-day juvenile fish growth test has been submitted to cover chronic toxicity to fish. This is not always recognised as a true chronic test in place of, e.g. a fish early life stage study, unless a clear justification has been provided. It may be that due to the low bioaccumulation potential and rapid dissipation to sediment that this test is suitable for fish - but this case should be made. It might be useful to include the surrogate acute approach to chronic fish classification to check whether this would affect the proposed chronic classification if the 28-day test is not used.				
Dossier Submitter's Response				
Please, see the first paragraph of the section 5.4:"For clarifications, all references on 8-HQS concentrations have not been included on the tables due to all analytical measurements in the experiments are for 8-HQ instead of 8-HQS. So the toxicity endpoints are expressed on 8-HQ measured and Beltanol-L nominal or calculated (from the actual content on the measured 8-HQ) concentrations."				

We are in agreement with the UK point that this test is not a strictly chronic test, but taking into account that all toxicity tests (acute and subchronic) were done on O. mykiss and that the toxicity pattern shown was an increase of the toxicity from acute to subchronic ("ACR = 200") assays it would be logic to suppose that in a chronic test on the same specie (O. mykiss) the toxicity will show at least a value (NOEC, ExC10) equal to the subchronic level. Therefore, according to previous reasoning and applying the precautionary principle we will remain our environmental classification proposal unmodified.

RAC's response

RAC believes that the comments raise some valid issues that have not been adequately addressed by the DS. There should be an explanation about why data from tests with the sulfate salt have been used for the substance itself (especially as there are questions about its degree of ionisation at neutral pH). The available fish NOEC is a "greater than or equal to" value as no effects were observed at the highest concentration tested, so it is not clear whether testing on more sensitive life stages would give a higher or lower NOEC. This testing artefact may also lead to a more stringent chronic classification than may actually be necessary.

Date	Country	Organisation	Type of Organisation	Comment number
06.11.2014	Belgium		MemberState	14

Comment received

Based on the results of the aquatic toxicity test on the most sensitive species (Desmodesmus subspicatus with 72hErC50=0.71mg/l, Oncorhynchus mykiss with 28dNOEC=0.010mg/l (TWA), the fact that the substance is considered as not rapidly degradable it is justified to classify, following the classification criteria of the regulation 1272/2008, as Aquatic Acute 1, H400 and Aquatic chronic 1, H410 . Furthermore, the substance shows no potential to bioaccumulate (log Kow<4).

In view of the proposed classification and toxicity band for acute toxicity between 0.1mg/l and 1mg/l, an M-factor for acute toxicity of 1 could be assigned and an M-factor for chronic toxicity of 10 (not rapidly degradable substance and NOEC=0.01mg/l)

In conclusion : we agree with the proposed environmental classification by the Spanish CA.

Some editorial or/and minor comments :
As no valid chronic data are available for algae, a chronic classification should be considered based on the lowest NOEC as well as on the lowest LC50 of the other trophic level (Desmodesmus subspicatus with 72hErC50=0.71mg/l) and classification should be based on the most stringent outcome. However in this case the most stringent outcome is achieved when considering the NOEC (same classification outcome, but difference in M-factor : M=10 when based on NOEC and M=1 when based on LC50)

Dossier Submitter's Response

Valid chronic data from the algae study can be found in the table 79 of the dossier (ErC10 = 0.21 mg/L) so we assume the comment is based on a misunderstanding. In any case the 28d NOEC from fish are more stringent and for this reason our proposal is based on the alga acute toxicity and the subchronic fish data.

RAC's response

Noted. The cited value for the ErC10 is incorrect – according to Table 48 in the CLP dossier, the correct value is 0.27 mg/L (the 0.21 mg/L result is for a yield endpoint).

ATTACHMENTS RECEIVED:

1. **Comments on the CLH report - Proposal for Harmonised Classification and Labelling, Substance Name: 8-hydroxyquinoline, Version 3, September 2014** – submitted by Probelte SA on 5 November 2014 (refer to comment 6)
2. **8-Hydroxyquinoline - Comments on the proposed classification and labelling according to the CLH report** – submitted by Probelte SA on 5 November 2014 (refer to comment 6)