Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

pirimiphos-methyl (ISO); *O*-[2-(diethylamino)-6-methylpyrimidin-4-yl] *O*,*O*-dimethyl phosphorothioate

EC Number: 249-528-5
CAS Number: 29232-93-7

CLH-O-0000001412-86-247/F

Adopted

30 December 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON PIRIMIPHOS-METHYL (ISO); *O*-[2-(DIETHYLAMINO)-6-METHYLPYRIMIDIN-4-YL] *O*,*O*-DIMETHYL PHOSPHOROTHIOATE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: pirimiphos-methyl (ISO); O-[2-(diethylamino)-6-methylpyrimidin-4-yl] O,O-dimethyl phosphorothioate
EC number: 249-528-5
CAS number: 29232-93-7
Dossier submitter: United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
13.04.2018	France		MemberState	1
Comment received				
- According to the RAR of the substance, the IUPAC name is O-2-diethylamino-6-methylpyrimidin-4-yl O,O- dimethylphosphorothioate. - According to the RAR of the substance, there are 4 relevant impurities, which are not confidential informations: R305032 max. 5 g/kg R65249 max. 5 g/kg R348532 max. 5 g/kg R305910 max. 5 g/kg R305032 : Thiophosphorochloridic acid O,O'-dimethyl ester R65249 : Thiophosphoric acid O,O'O''-trimethyl ester R348532: Thiophosphoric acid O,S,O'-trimethyl ester R305910: Dithiophosphoric acid O,S,O'-trimethyl ester				
Dossier Submitter's Response				
Noted. The correct name of *O*-[2-(diethylamino)-6-methylpyrimidin-4-yl] *O*,*O*-dimethyl phosphorothioate was provided by ECHA during the accordance check. Regarding the 4 relevent impurities, only one (R305032) has an entry in the C&L inventory. It is listed with the following self-classification (49/73 entries): Acute Tox. 4 (H302) Acute Tox 4. (H312) Acute Tox. 1 (H330)				

Skin irrit. 2 (H315) Eye Dam. 1 (H318) STOT SE 3 (H335) Aquatic Chronic 3 (H412) R305032 can be present in pirimiphos-methyl at ≤ 0.5 %. Given the concentration of this impurity, it is not considered to impact on the proposed classification and labelling.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
03.04.2018	Germany		MemberState	2
Comment received				
The German CA agrees with the proposed classification.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
03.04.2018	Germany		MemberState	3
Comment received				
The two carcinogenicity studies presented / available (1 rat, 1 mouse) have several shortcomings limiting the reliability of the studies. In particular, for the study in rats uncertainty lies in the number of animals investigated, also a statistical analysis of the data is not given. For the study in mice, the initially chosen top dose of 400 ppm was inadequate. There was a significant higher number of islet cell adenoma in male rats of the top dose compared to concurrent control and outside the HCD 1965-1973. The effect was clearly dose dependent, with p=0.0004 in the Cochrane Armitage linear trend test (data from Table 8 on page 15). The use of the HCD studies 1984-2004 is not compliant. The positive results on carcinogenicity in rats (islet cell adenoma and carcinoma (pancreas), meningioma (brain)) should be discussed in more detail considering the weight of evidence, e.g. the lack of genotoxicity, or that there were no reported pre neoplastic lesions in the brain in any of the repeat dose studies.				
Dossier Submitter's Response				
Thank you for your comment. In the CLH report we note that the number of animals investigated in the rat study leave some uncertainties. However, we do not believe this leads to a significant problem regarding the interpretation of the results as the number of animals were comparable across all dose groups (including the control). We also agree that the more recent HCD studies are not contemporary to the study being evaluated, however, on the basis that many of the findings observed were considered rare, the DS believes that the extended HCD still provides useful information. The top dose in mice was originally 400 ppm but was reduced to 300 ppm (57 mg/kg bw/day) after the first week due to bodyweight loss. There were a number of early deaths at the mid and top dose, thought to be caused by anticholinesterase effects, nephropathy				

or urinary bladder obstruction. The top dose in mice was approximately 4.5 times higher than the equivalent dose in rats. Regarding the pancreatic islet cell adenoma observed in male rats. There were 4/42 animals observed with these benign tumours (9.5 %). This was indeed above the concurrent control (0/42) and the HCD (1965-1973): 0 – 6 %. It was just within the extended HCD (1984 – 2004): 0 – 9.6 %. As mentioned above, the DS understands this is data was not taken from a 5 year period around the carcinogenicity study but believes it is of relevance in this case. The DS does not agree that this finding can be considered dose-dependent as there are no such findings observed in any of the lower treatment groups. The dossier submitter concludes that the tumours observed in the pancreas and brains of rats occurred spontaneously and were not related to treatment with pirimiphos-methyl. There were no pre-neoplastic lesions or any other toxicological findings that indicated these tissues were a target organ and no mechanistic basis for tumour formation, raising into question the biological plausibility of the findings. Furthermore, pirimiphos-methyl was found to be non-genotoxic in a battery of *in vitro* and *in vivo* tests and in a robust carcinogenicity study in mice, using higher doses, no tumours were observed.
RAC's response
RAC agrees with the DS that the observed marginal increases in some tumour types in one sex of rats do not warrant classification.

Date	Country	Organisation	Type of Organisation	Comment number
06.04.2018	Spain		MemberState	4
Comment received				
The Spanish CA agreed with the dossier submitter that tumours observed in the pancreas and brains of rats occurred spontaneously and were not related to treatment with pirimiphos-methyl. There were no pre-neoplastic lesions or any other toxicological findings that indicated these tissues were a target organ. Furthermore, pirimiphos-methyl was found to be non-genotoxic in a battery of in vitro and in vivo tests and in a robust carcinogenicity study in mice, using higher doses, no tumours were observed. Therefore, on the basis of the available evidence, pirimiphos-methyl should not be classified for carcinogenicity.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
09.04.2018	United Kingdom	Syngenta	Company-Manufacturer	5
Comment received				
9.12 Carcinogenicity Syngenta support the conclusion that pirimiphos methyl should not be classified for carcinogenicity. The historical control data from the conducting laboratory that were				

submitted most recently to support the EU re-registration support the conclusion that there are no treatment related neoplastic findings in the rat carcinogenicity study.
Dossier Submitter's Response
Noted. Thank you.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
13.04.2018	France		MemberState	6
Comment received				
Classification Carc cat 3 R40 was proposed for the 1rst approval of pirimiphos-methyl as a pesticide active substance at European level. It was based on brain and pancreas tumours increased incidences in rats at the highest dose tested (300 ppm, i.e. 15 mg/kg/d) outside the HCD values. FR is of the opinion to maintain this classification proposal, as a Carc cat 2 H351 GHS translation. Indeed, - While increased incidences were not statistically significant, it is noteworthy that less than 50 animals of each sex were tested by dose (contrary to what the OECD guideline N° 451 (2009) recommends) decreasing the statistical robustness, - despite the fact that the new HCD provided for pancreas and brain tumours is from the same laboratory and uses the same strain of rat as in the Gore (1974) study, they are not contemporary wth the study since they cover a period from 1984 to 2004, which limits their relevance (refer to Regulation (EU) N° 283/2013), - Since pirimiphos-methyl is a molecule with neurological tropism (cholinesterase inhibition activity), the increased incidences of several different types of brain tumours (meningioma, ependymoma and ganglioneuroma) reported beyond the maximal original HCD values should raise particular concerns.				
Dossier Submitter's Response				
Noted. No statistical analysis was conducted therefore we can not comment on the statistical robustness. It is noted that the study predates OECD and GLP and that the number of animals investigated leaves some uncertainties. However, we do not believe this leads to a significant problem regarding the interpretation of the results as the number of animals were comparable across all dose groups (including the control). We agree that the HCD data between the period of 1984 – 2004 are not contemporary to the study. However, we believe that due to the rare nature of some of the findings, the HCD provides some reassurance that these types of tumours can occur spontaneously in rats. We don't agree that the findings in the brain provide sufficient evidence of a carcinogenic response and stand by our arguments presented in the CLH.				
RAC's response				
RAC agrees with the DS that the observed marginal increases in some tumour types in one sex of rats do not warrant classification.				

Date	Country	Organisation	Type of Organisation	Comment number
11.04.2018	Italy	Federchimica	Industry or trade association	7
Comment received				
9.12 Carcinogenicity Federchimica supports the conclusion that pirimiphos methyl should not be classified for carcinogenicity. The historical control data from the conducting laboratory that were submitted most recently to support the EU re-registration support the conclusion that there are no treatment related neoplastic findings in the rat carcinogenicity study.				
Dossier Submitter's Response				
Noted, thank you.				
RAC's response				
Noted.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
09.04.2018	United Kingdom	Syngenta	Company-Manufacturer	8
Comment received				
9.11 Germ cell mutagenicity Syngenta support the conclusion that pirimiphos methyl should not be classified for germ cell mutagenicity. There are two additional genotoxicity studies available, both of which were negative, and are summarised briefly below. These have also been made available to the EU registration review process. These new data support the position that pirimiphos methyl is not genotoxic. 9.11.1.1 Genotoxicity In vitro studies Pirimiphos-methyl has been tested in a mammalian cell gene mutation assay in Chinese hamster V79 cells in vitro (V79/HPRT) in accordance with OECD test guideline 476 (2016), which shows pirimiphos methyl is not mutagenic in the HPRT assay. The full study report and robust study summary can be provided on request. 9.11.1.2 Genotoxicity In vivo studies in somatic cells Pirimiphos-methyl has been tested in a micronucleus test in the mouse in accordance with OECD test guideline 474 (2016), which shows pirimiphos-methyl is non-genotoxic. The full study report and robust study summary can be provided on request.				
Dossier Submitter's Response				
Noted, thank you. Unfortunately, these studies were not provided to the UK CA in time for inclusion in the RAR and so have not yet been evaluated under the renewal process. Briefly: In the guideline *in vitro* gene mutation assay, pirimiphos methyldid not induce gene mutations at the HPRT locus in V79 cells of the Chinese hamster in the presence and absence of metabolic activation. The results of this study are therefore negative for mutagenicity.				

In the guideline *in vivo* micronucleus test, carried out in male CD-1 mice, pirimiphos-methyl was administered orally at concentrations of 0, 175, 350 and 700 mg/kg bw. Animals were sacrificed at 24 or 48 h after dosing. The bone marrow was extracted and smear preparations were made and stained. Polychromatic (PCE) and normochromatic (NCE) erythrocytes were scored for the presence of micronuclei. Following dosing, hunched posture, ptosis, lethargy, ataxia, splayed gait, hypothermia, elevated tail, decreased respiratory rate, laboured respiration, increased salivation, occasional body tremors, loss of righting reflex, and increased respiratory rate were observed in animals of the top dose group to a varying degree. Analysis of the plasma and blood cell samples indicated that bone marrow exposure was most likely. There were no marked decreases in the PCE/NCE ratio observed after 24 or 48 hours when compared to the vehicle control group. These two studies are in support of the other negative data for mutagenicity.
RAC's response
RAC evaluated the original study reports of the two new studies, concluding that the *in vivo* micronucleus study is indeed negative. The *in vitro* HPRT test is however concluded to be positive in the presence of metabolic activation; without metabolic activation it is clearly negative.

Date	Country	Organisation	Type of Organisation	Comment number
13.04.2018	France		MemberState	9
Comment received				
It should be noted that in volume 3 – B6 of the draft renewal assessment report on Pirimiphos-methyl (UK, 2017), among the literature that reported many positive results from in vitro bacterial mutation genotoxicity tests, the reference Moriya (1983) has also been cited, whereas not reported in the present CLH report (UK, 2017). Additionally, the sister chromatid exchange assay (Howard (1986)), was concluded to be equivocal in RAR rather than negative (CLH), considering the statistically significant increases in SCE/cell seen in the absence and presence of metabolic activation. It is noteworthy in the context of the renewal, 2 new genotoxic tests have been initiated: an in vitro mammalian gene mutation assay and an in vivo mammalian erythrocyte micronucleus assay compliant with the current test guidelines, but were not finalized at the time the CLH report was submitted. The final reports should be currently available to RMS (expected submission in August 2017). These new studies should be submitted and assessed before definitively rule on the genotoxic potential of the active substance (positive/equivocal responses reported in many of the dated studies, performed before 1998).				
Dossier Submitter's Response				
Noted. A summary of the sister chromatid exchange study by Howard et al (1986) was considered in the CLH, however on the basis that this study is no longer considered a guideline study, its use was to add to the weight of evidence only. Following consideration of the results provided, which appeared to be extremely variable between cultures, the DS believed that the results were negative rather than equivocal. There did				

not appear to be a clear, dose-related increase in mean number of SCEs in the presence or absence of S9.

Please see the response to comment 8 with regards to the newly submitted genotoxicity studies.

RAC's response

RAC considers that the interpretation of the SCE study by Howard (1986) as either negative or equivocal will not affect the overall conclusion of the proposed classification, as the SCE is an *in vitro* study and either outcome does not contradict the results of the other *in vitro* and *in vivo* tests.

Please see the response to comment 8 with regards to the newly submitted genotoxicity studies.

Date	Country	Organisation	Type of Organisation	Comment number
11.04.2018	Italy	Federchimica	Industry or trade association	10

Comment received

9.11 Germ cell mutagenicity
Federchimica supports the conclusion that pirimiphos methyl should not be classified for germ cell mutagenicity. There are two additional genotoxicity studies available, both of which were negative, and are summarised briefly below. These have also been made available to the EU registration review process. These new data support the position that pirimiphos methyl is not genotoxic.

9.11.1.1 Genotoxicity In vitro studies
Pirimiphos-methyl has been tested in a mammalian cell gene mutation assay in Chinese hamster V79 cells in vitro (V79/HPRT) in accordance with OECD test guideline 476 (2016), which shows pirimiphos methyl is not mutagenic in the HPRT assay. The full study report and robust study summary (document PP511_10245 "Pirimiphos-methyl - In Vitro Gene Mutation Assay - Chinese Hamster" and PP511_10247 "In Vitro Gene Mutation Assay Study Summary") will be provided if requested at a later time.

9.11.1.2 Genotoxicity In vivo studies in somatic cells
Applicant: Pirimiphos-methyl has been tested in a micronucleus test in the mouse in accordance with OECD test guideline 474 (2016), which shows pirimiphos-methyl is non-genotoxic. The full study report and robust study summary (document PP511_10246 "Pirimiphos-methyl - Micronucleus Test - Mouse" and PP511_10262 "Micronucleus Test Study Summary") will be provided if requested at a later time.

Dossier Submitter's Response

Noted, thank you. Please see response to comment 8.

RAC's response

Noted. Please see response to comment 8.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
06.04.2018	Spain		MemberState	11
Comment received				
Pirimiphos- methyl has a minimum classification for Acute Tox. 4*; H302 in Annex VI to CLP entry arising from translation of classifications listed in Annex I to directive 67/548/EEC. In the CLH report the dossier submitter has address the removal of this minimum classification. The acute oral toxicity of pirimiphos-methyl has been investigated in one study in rats. The oral LD50 value of 1414 mg/kg bw in rats is within the range 300< LD50 ≤ 2000 for classification as Acute Tox 4, H302 harmful if swallowed. The Spanish CA agreed with this classification.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
09.04.2018	United Kingdom	Syngenta	Company-Manufacturer	12
Comment received				
9.15.2 Comparison with CLP criteria Although pirimiphos-methyl clearly produces inhibition of acetylcholinesterase in brain and erythrocytes at relatively low doses, this inhibition is rarely associated with any clinical effects. This inhibition is seen after both single and repeated dose, and there is no clear evidence that the effect increases with increased duration of dosing. Hence it is unclear whether the cholinesterase inhibition seen in longer term studies is an acute or repeat dose effect. On this basis, Syngenta propose that a STOT-SE classification may be more appropriate than a STOT-RE classification. This proposal would be consistent with the RAC opinion for another organophosphate, phosmet (RAC opinion 3rd June 2016), which has a very similar pattern of acetylcholinesterase inhibition. The RAC rationale for STOT-SE for phosmet was based on the following points: • in studies other than acute, clinical signs typical for organophosphate poisoning were rarely described, despite inhibition of RBC and brain AChE up to 100% • it is unclear whether the symptoms related to cholinergic inhibition appeared following repeated exposure or already as a response to the first exposure • regarding cholinesterase inhibition, evidence of accumulation of effects with repeated dosing is limited Therefore a conclusion of STOT-SE 1 for pirimiphos-methyl would be consistent with the				

opinion for phosmet.
Dossier Submitter's Response
Thank you for your comment, we note the RAC opinion of phosmet. However, in the available repeated dose studies, the finding of acetylcholinesterase inhibition occurs at very low doses (from doses as low as 1 mg/kg bw/day in a two-generation study in rats). As noted in the CLH report, we remain of the opinion that these data support classification with STOT-RE rather than STOT-SE.
RAC's response
Whereas there are indeed some similarities in the toxicity profile between the two acetylcholinesterase inhibitors pirimiphos-methyl and phosmet, RAC notes also some differences. For phosmet, the level of acetylcholinesterase inhibition induced by a single dose was at the same or higher level as that of a similar dose level in studies of longer duration. For pirimiphos-methyl the opposite is the case. Furthermore, phosmet induced clinical signs typical for organophosphate exposure at a lower acute dose than the doses triggering the acute oral toxicity classification for phosmet. For pirimiphos-methyl, such clinical signs were observed within the dose-range triggering its acute oral toxicity classification. RAC agrees with the DS that the effects observed in the repeated dose studies should be considered for classification with STOT RE because a comparison of the effects after acute and repeated exposure shows that more severe effects occur after repeated exposure than after acute exposure at comparable dose levels.

Date	Country	Organisation	Type of Organisation	Comment number
06.04.2018	Spain		MemberState	13
Comment received				
Erythrocyte and brain cholinesterase activity were reduced to levels considered to be adverse (> 20 %) in all 90-day oral studies in rats and mice and in the two year feeding studies in rats, mice and dogs. There was also evidence of acetylcholinesterase inhibition in a 21 days dermal study in rabbits. The effects observed in the repeated dosing study occurred at doses much lower than those used in the acute toxicity study. In the majority of studies, the reduction in erythrocyte and brain cholinesterase activity was not accompanied by adverse clinical effects and there was no reported evidence of neurological effects in any study. However, significant inhibition of brain and erythrocyte acetylcholinesterase by 20 % or more alone represents a clear toxicological effect and is deemed relevant enough for classification purposes. In both rats and mice dosed orally for 90 days and in rabbits treated dermally for 21 days, effects occurred at doses relevant for classification with STOT-RE 1 that were not always found to be reversible (≤ 10 mg/kg bw/day for a 90 day oral study and ≤ 85 mg/kg bw/day for a 21 day dermal study). Therefore, the Spanish CA agrees with the proposal of the dossier submitter to classifiy pirimiphos-methyl with STOT-RE 1 H372: Causes damage to organs (inhibition of acetylcholinesterase activity) through prolonged or repeated exposure.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON PIRIMIPHOS-METHYL (ISO); *O*-[2-(DIETHYLAMINO)-6-METHYLPYRIMIDIN-4-YL] *O*,*O*-DIMETHYL PHOSPHOROTHIOATE

Date	Country	Organisation	Type of Organisation	Comment number
11.04.2018	Italy	Federchimica	Industry or trade association	14
Comment received				
9.15.2 Comparison with CLP criteria Although pirimiphos-methyl clearly produces inhibition of acetylcholinesterase in brain and erythrocytes at relatively low doses, this inhibition is rarely associated with any clinical effects. This inhibition is seen after both single and repeated dose, and there is no clear evidence that the effect increases with increased duration of dosing. Hence it is unclear whether the cholinesterase inhibition seen in longer term studies is an acute or repeat dose effect. On this basis, Federchimica proposes that a STOT-SE classification may be more appropriate than a STOT-RE classification. This proposal would be consistent with the RAC opinion for another organophosphate, phosmet (RAC opinion 3rd June 2016), which has a very similar pattern of acetylcholinesterase inhibition. The RAC rationale for STOT-SE for phosmet was based on the following points: • in studies other than acute, clinical signs typical for organophosphate poisoning were rarely described, despite inhibition of RBC and brain AChE up to 100% • it is unclear whether the symptoms related to cholinergic inhibition appeared following repeated exposure or already as a response to the first exposure • regarding cholinesterase inhibition, evidence of accumulation of effects with repeated dosing is limited Therefore a conclusion of STOT-SE 1 for pirimiphos-methyl would be consistent with the opinion for phosmet.				
Dossier Submitter's Response				
Thank you. Please see the response to comment number 12.				
RAC's response				
Noted. Please see response to comment 12.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
13.04.2018	France		MemberState	15
Comment received				
FR agrees with the classification and M factors (acute and chronic) proposals.				
Dossier Submitter's Response				
Noted, thank you.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
09.04.2018	United Kingdom	Syngenta	Company-Manufacturer	16
Comment received				
Syngenta agrees with the evaluation and proposals for classification and labelling with respect to environmental hazard.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
13.04.2018	Finland		MemberState	17
Comment received				
FI CA supports the conclusions that the substance is potentionally bioaccumulative (log Kow > 4 & BCFss > 500) and not rapidly degradable (< 70 % degradation within 28 days). The key studies for this proposal are Daphnia sp. acute immobilization test (OECD 202) and Daphnia magna reproduction test (OECD 211) which are considered valid for classification purposes of aquatic hazards. According to the studies with the substance, pirimiphos-methyl, the acute toxicity EC50 value is between 0.1-1 µg/L and the chronic toxicity NOEC value is between 0.01-0.1 µg/L, resulting in M-factors of 1000. Based on the classification criteria, FI CA supports updating the current classification of Aquatic Acute 1, H400 by adding M-factor of 1000 and Aquatic Chronic 1, H410 by adding M-factor of 1000.				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
13.04.2018	Belgium		MemberState	18
Comment received				
BE CA supports the proposed environmental classification for Pirimiphos-methyl : Aquatic Acute 1, 400 ; Macute = 1000 and Aquatic Chronic 1, H410; Mchronic=1000. Some editorial or/and minor comments : Aquatic Acute and chronic toxicity for algae : in the description of the Smyth et al (1989) study it is mentioned that the study was performed to OECD201 and GLP compliant, while in table 14 and 15 the study is non-guideline and non-GLP.				
Dossier Submitter's Response				
Noted. Thank you. There is an error in tables 14 and 15. The Smyth (1989) study was performed to OECD201 and was GLP compliant.				

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
03.04.2018	Germany		MemberState	19
Comment received				
Regarding Section 10.4.2 "Measured partition coefficient and bioaccumulation test data": The test species of the bioconcentration study, Anon. (2007,) rainbow trout (Oncorhynchus mykiss) given in the text does not match the species given in the RAR. The RAR stated the warm water species ricefish (Oryzias latipes) with the same BCF values. (study: Seo, J. (2007). Please clarifiy.				
Dossier Submitter's Response				
Noted. Thank you. There is an error in the CLH report, the highlighted study was conducted in Oryzias latipes.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
11.04.2018	Italy	Federchimica	Industry or trade association	20
Comment received				
Federchimica agrees with the evaluation and proposals for classification and labelling with respect to environmental hazard				
Dossier Submitter's Response				
Thank you.				
RAC's response				
Noted.				