Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

***N*-methoxy-*N*-[1-methyl-2-(2,4,6-trichlorophenyl)-ethyl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxamide; pydiflumetofen**

EC Number: -
CAS Number: 1228284-64-7

CLH-O-0000001412-86-271/F

Adopted

15 March 2019

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON *N*-METHOXY-*N*-[1-METHYL-2-(2,4,6-TRICHLOROPHENYL)-ETHYL]-3-(DIFLUOROMETHYL)-1-METHYLPYRAZOLE-4-CARBOXAMIDE; PYDIFLUMETOFEN

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: *N*-methoxy-*N*-[1-methyl-2-(2,4,6-trichlorophenyl)-ethyl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxamide; pydiflumetofen
EC number: -
CAS number: 1228284-64-7
Dossier submitter: France

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
08.06.2018	Switzerland	Syngenta Crop Protection AG	Company-Manufacturer	1
Comment received				
Syngenta supports the classification as proposed by the dossier submitter France. Additional information that has also recently been submitted into the review of this new active substance under Regulation 1107/2009 is herewith provided. It is related to the hazard classes Mutagenicity and Reproductive Toxicity. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 20180608 CLH submission pydiflumetofen - non-confidential.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20180608 CLH submission pydiflumetofen - confidential.zip				
Dossier Submitter's Response				
Additional information submitted in the framework of the peer review process of pydiflumetofen under Regulation 1107/2009 has been included and assessed by the DS in the revised DAR.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
08.06.2018	Belgium		MemberState	2
Comment received				
BECA thanks FRCA for the CLH proposal and the use of the combined DAR-CLP template.				

Dossier Submitter's Response
Noted, thank you.
RAC's response
Noted.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
29.05.2018	Germany		MemberState	3
Comment received				
The German CA proposes a classification of pydiflumetofen as Carc 2, H351: There was a significant increase in liver cell adenoma and carcinoma in high dose male mice and a higher incidence (even though not gaining statistical significance) of both tumours was observed at the mid dose level already. There is good evidence that the mechanism behind is CAR-mediated. However, it was noted that CAR activation was also demonstrated in rats. One would expect liver cell proliferation and perhaps also tumour formation also in the rat. In other studies, the liver was in fact a target organ. Now, there are two lines of reasoning. On one hand, it cannot be excluded that further modes of action of unknown human relevance are involved in tumour formation in male mice. On the other hand, the absence of a similar neoplastic effect in the rat might be due to the rather low dose levels (up to 100 or 300 mg/kg bw/day in female/male rats) in the long-term study. In line with that, the DS itself expressed some doubts whether the top dose level in particular in the long-term study in rats was in fact sufficiently high to assess a carcinogenic potential of concern. The argument that the MTD was reached in this study is not convincing since a body weight reduction by 18 or 9% is not that much impressive. To conclude, pydiflumetofen proved carcinogenic in male mice, due to one or several mode(s) of action of equivocal human relevance, whereas carcinogenicity in the rat was not sufficiently investigated. A proposal for classification (Carc 2, H351) seems most appropriate. In addition, it should be taken into consideration that the main metabolite of pydiflumetofen, i.e., 2,4,6-TCP, has been classified as Cat 2 carcinogen in the EU and is also considered carcinogenic by U.S. EPA and IARC.				
Dossier Submitter's Response				
The DS is of opinion that although the dose levels selected for the long term/carcinogenicity study in rat are rather low, it can be considered that the MTD has been reached. Indeed, significant treatment-related decreases were observed in body weight gains in high dose males (↓18%) and high dose females (↓13%). Additionaly at this dose, it was observed significant increases in absolute and relative liver weight associated with hepatocellular hypertrophy in both sexes and liver eosinophilic inclusions in males. According to OECD (2012), the top dose selected in a long-term study should ideally provide some signs of toxicity (such as slight depression of body weight gain (not more than 10%)), without causing e.g., tissue necrosis or metabolic saturation and without substantially altering normal life span due to effects other than tumors. The DS agrees that the major metabolite 2,4,6-TCP classified as carcinogen by several international instances must be taken into consideration. In this context, the DS proposed in the DAR/CLH report, a prediction of the systemic exposure of 2,4,6 TCP (and its related metabolites) following oral administration of doses of pydiflumetofen higher than those tested in the 2-year rat study (> 300 and up to 1000 mg/kg bw/day). To attain a systemic exposure of TCP which might causes 25% of leukemia in the rat (T25) (dose				

calculated from NTP study data performed with 2,4,6-TCP (NCI 1979)), the rats should be orally exposed to 1000 mg/kg bw/day of pydiflumetofen.
DS considers that the proposed MOA leading to liver tumors in mice (through CAR activation) is sufficiently substanciated by mechanistic studies which supports the non-relevance for human.However, it is noteworthy that scientific researchers belonging to French research institutes and hospital doctors specialising in genetic diseases related to succinate dehydrogenase (SDH) deficiencies have raised a high concern regarding the use of SDHI (succinate dehydrogenase inhibitor) as fungicides in agriculture. Indeed the impaired SDH activity caused by genetic variants can induce severe human neurological diseases, or can lead to the development of tumors and/or cancers.
ANSES decided to set up an emergency expert group to analyse the alert issued, and to identify whether immediate actions or additional risk management measures for the active substances and related products containing SDHI active substances should be taken.
Its conclusions are expected in September-October 2018.
ANSES has informed EFSA, ECHA, DG Heath and Food Safety and Competent Authorities by post and email. It should be noted that this alert does not concern only pydiflumetofen but is related to all the active sustances sharing this same fungicide mode of action via the inhibition of succinate dehydrogenase (SDHI chemical class fungicide).

RAC's response

RAC agrees that technically the MTD has been reached so according to guidance the rat long-term study has been performed to adequate requirements. RAC sympathises with the MSCA and believes the dosing regime employed in the rat long-term study could have been dosed higher. Females for instance were dosed too low for the regime to end at 100 mg/kg/day where there is evidence of an increase in thyroid adenomas but only at the higher limit of the HCD range. We have only the data that has been presented to us in the available studies and that is a positive tumourigenic response in one species (mouse) and not in the other (rat) by a mechanism supported by mechanistic data and believed to have little relevance for human hazard assessment. It is often the case that mechanistic studies generate data where CAR-mediated responses are confined or shown to operate in one of the rodent species and not both, though it is generally accepted that the mechanism is plausible in both rats and mice. The lack of response in one species is therefore not always surprising nor is it a prerequisite to accept classification.

As regards the metabolite 2,4,6-TCP, there is no data to indicate that a sufficiently high dose of parent active substance was tested in the long-term study to elicit the carcinogenic potential of its major circulating metabolite. The carcinogenicity of the metabolite has not been adequately assessed.

On the weight of the presented evidence, a CAR mode of action is considered to be the most plausible explanation for the increase in liver adenomas and carcinomas in the male mouse. However, the shortcomings in the hepatocyte studies, in combination with the other uncertainties (such as selection of doses in both rats and mice, possible treatment-relationship of thyroid adenoma/hyperplasia observed in female rats, absence of MoA data for female rats, possible involvement of carcinogenic metabolite 2,4,6-TCP) need to be considered. A weight of evidence assessment by RAC consideres that it is not conclusively shown that the tumours are of no relevance to humans.

The debate within the French regulatory authority and between EFSA concerning the engineered mechanism of action in target species, i.e. succinate dehydrogenase inhibition and its implications for non target organisms is beyond RAC's remit and outside of the scope for classification and labelling in this case. There was no evidence from the

pydiflumetofen repeated dose toxicity database, to indicate an effect of concern at relevant exposures, that this SDHI fungicide should pose a hazardous threat to health from inhibition of mitochondrial respiratory complex II within non-target organisms such as mammals or humans.

Date	Country	Organisation	Type of Organisation	Comment number
08.06.2018	Denmark		MemberState	4

Comment received

DEPA's comments to the DAR:
Rat: On page 285 it is stated that for thyroid follicular cell adenomas, the historical control range was 0-10%. However, it seems from table 6.5-16 as if the range in females is 0-3.9%, and therefore the incidence of these adenomas in females at 1500 ppm of 3/51x100%=5.9% is actually outside the HCD. These adenomas may be considered to be related to treatment with pydiflumetofen and a NOAEL for carcinogenicity in females may be considered at 450 ppm.

Mouse: In the mouse carcinogenicity study, an increase in eosinophilic foci of cellular alteration in the liver of males was observed. Foci are presumptive preneoplastic lesions according to NTP (https://ntp.niehs.nih.gov/nnl/hepatobiliary/liver/foci/liver-foci_508.pdf) and it may therefore be discussed further if the foci observed from 75 ppm, which are outside HCD range, should be considered treatment-related and adverse (leading to a NOAEL <75 ppm in males). Maybe the statistical significance of the total incidences and incidences termed "moderate" could be analysed using a trend test? In a 28 day mouse MOA study (p. 305), PROD activities and DNA synthesis were increased (1.6 to 2.4-fold and up to 5.6-fold, respectively) in mice dosed with 75 ppm, suggesting that the foci may be treatment-related.

Dossier Submitter's Response

RAT

The HCD range of 0-10% corresponds to the background incidence of thyroid cell adenomas in females from 19 carcinogenicity (104-weeks) dietary rat studies provided by the performing laboratory between 2001 and 2013. One study performed in 2005 showed an incidence of 5/50 (10%). However, if we take into account of the 5-year time frame only (8 studies; 2009-2013), the background incidence is 0-3.9%.
During the peer review process under Regulation 1107/2009, the applicant submitted updated historical control data including two additional 104-week studies performed in 2013 and 2015 in female Hans Wistar rats at Charles River laboratories. Taking into account a 5-year time frame only (7 studies; 2009-2013), the background incidence is 0-5.8% (3/52) (as presented in Table 6.5-16 in the revised DAR). Thus, the increase in the incidence of thyroid follicular cell adenomas observed at 1500 ppm in females (3/51 (5.9%) vs 1/51 (2%) in control) can be considered within the historical controls provided by the performing laboratory in the 5-year time frame. To support that the thyroid follicular cell adenomas observed in females at the higher dose can be considered not treatment related, it should be noted that there were no preneoplastic lesions (hyperplasia) observed at 12 or 24 months in the long term study and no histopathological findings were observed in thyroid in females in other rat toxicity studies (28/90 days and 2 Generations). In addition, the incidence of thyroid follicular adenomas in female rats after administration of pydiflumetofen was not statistically significantly different to controls and there was no dose response (peto analysis). It was also shown

that pydiflumetofen does not have a direct effect on thyroid peroxidase in the rat (*in vitro*) and therefore, pydiflumetofen is not acting via a direct effect on the thyroid (data presented in DAR B 6.8.2).

MOUSE

During the peer review process under Regulation 1107/2009 and following an EFSA request, the applicant submitted new HCD for eosinophilic foci of cellular alteration in the liver of male mice from long-term studies performed during a larger period from 2007 to 2013 (total of nine 80-week mouse studies). With this new data, the incidence of eosinophilic foci at 75 ppm (8%) is still outside the range of this HCD (0-6%).
However, it should be noted that the increase in eosinophilic foci in liver of male mice treated with 75 ppm is not statistically significant compared to the control group, the increase being statistically significant only at the higher dose of 2250 ppm. No peto trend analysis was performed by the applicant regarding the total incidence for this parameter which leads difficult the interpretation of this effect slightly above the HCD at 75 ppm.
Foci of cellular alteration represents small to large aggregates of tinctorially distinct hepatocytes within the hepatic parenchyma and are sometimes considered putative preneoplastic lesions. Foci of hepatocellular alteration increase with age in mice and may be induced by treatment in younger rodents. All types of foci (eosinophilic, basophilic and clear cell foci) are more common in male than in female mice. In this study, the eosinophilic foci were the only type of foci observed and they were only seen in males. They occurred in terminal animals and not in preterminal death/decedent animals, which could be indicating that there is no early occurrence or reduction in latency. In addition, it is noteworthy that eosinophilic foci were not observed in the 90 day mouse study where only an increase in hepatic centrilobular hypertrophy was noted with no evidence of hepatic necrosis. Thus, the biologic relevance of this effect slightly above the HCD observed at 75 ppm at the end of the experiment is questionable. In the mouse database, a very weak proliferative signal after exposure to 75 ppm SYN545974 was observed in the 28 day investigative study, however this key event occurred in isolation, and no statistically-significant increases in surrogate markers of CAR activation (Cyp2b10 mediated PROD activity) and no increases in mitosis (see Table 6.5-27 in the DAR). In addition, no alterations in liver weight or histopathology in the 90-d study were observed at the low dose of 100 ppm. In this present study (80 week carcinogenicity study), consistent with what was observed in the short term studies, no effects on liver weight were observed and ultimately, no increases in tumour incidence were observed at this low dose level (75 ppm).
Taking into account all these elements, the DS is of opinion that that the marginal increase of eosinophilic foci observed at 75 ppm can be considered not related to treatment and the NOAEL can be set at 75 ppm.

RAC's response

RAC notes the more recent and more relevant HCD described by the DS and incorporated into the DAR by the RMS. RAC agrees that the increase in the incidence of thyroid follicular cell adenomas observed at 1500 ppm in females (3/51 (5.9%) vs 1/51 (2%) in control) can be considered as being within the historical control range. It is more difficult to decide if a treatment related effect was observed or not. The top dose in females (102 mg/kg/day) was too low. A higher dose would have confirmed the presence or absence of a dose response relationship or substance related effect. RAC notes that males did not show an increased incidence of thyroid tumours relative to controls when tested at 288 mg/kg/day. RAC agrees with the DS, that there was no supporting data from histopathology or other studies to consider pydiflumetofen a carcinogen in relation to the rat thyroid.

RAC notes the comments on NOAEL setting but it is not relevant for classification.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
29.05.2018	Germany		MemberState	5
Comment received				
In its peer review on the DAR in 2017, the German CA did not support the proposed request of a Comet assay. The outcome of the EU expert discussion (PRAS) must be awaited. For the time being, we support the proposal not to classify pydiflumetofen for mutagenic effects.				
Dossier Submitter's Response				
During the review process under Regulation 1107/2009 of this new active substance, an additional in vivo genotoxicity assay (rat bone marrow chromosome aberration test) has been submitted and was negative. For all *in vivo* genotoxicity assays (rat and mice), the bone marrow have been sufficiently exposed and clastogenicity and aneugenicity have been adequately assessed: pydiflumetofen was detected in significant amount in blood (Cmax= 845 mg/ml (mice) and 612 mg/ml (rat)) up to 24h. However, considering that: - Pydiflumetofen is clastogenic *in vitro* in absence of metabolic activation and - Liver tumors are observed in mice and - Number of *in vitro* studies from the literature indicate that the major metabolite of pydiflumetofen (blood/urine), 2,4,6-TCP, is weakly aneugenic and clastogenic *in vitro* and the limited database of *in vivo* studies is contradictory*: negative results in rats (alkaline elution assay-liver and WBC) but positive results in mice (in vivo COMET assay, spot test) and in Zebrafish (liver p53 gene assay),* the DS was questioning in the DAR on the need of a confirmatory *in vivo* assay on pydiflumetofen. In the opinion of the DS, the more adequate test should be an *in vivo* COMET assay to be performed on an organ from the GI tract and liver. Indeed, this additional test would allow to definitely exclude the possibility of a genotoxic mode of action for the liver tumors and to ensure of the absence of genotoxicity on a local tissue exposed upstream liver metabolism (e.i. gastrointestinal tract). The result of this study could also cover the genotoxicity of the major metabolite of pydiflumetofen, 2,4,6 TCP for which only very limited data are currently available *in vivo*. Discussion regarding the issue regarding the need of a confirmatory in vivo assay will take place during the EU expert discussion (PRAS) in September 2018.				
RAC's response				
RAC agrees with the proposal not to classify pydiflumetofen for mutagenic effects.				

Date	Country	Organisation	Type of Organisation	Comment number
08.06.2018	Switzerland	Syngenta Crop Protection AG	Company-Manufacturer	6
Comment received				
To support regulatory requirements in other regions, a second in vivo genotoxicity study has been conducted on SYN545974. A rat bone marrow chromosome aberration assay				

was conducted in 2017 on the batch of material (SMU2EP12007) that gave a positive response in the in vitro chromosome aberration test in human lymphocytes. SYN545974 did not induce chromosome aberrations in the bone marrow cells of rats when tested up to 2000 mg/kg. The summary of this study is attached, the study report can be provided upon request.

The in vivo rat bone marrow chromosome aberration test did not include an assessment of bone marrow exposure to SYN545974. However, it is known that SYN545974 is systemically available in the rat, following oral gavage dosing, as demonstrated in the absorption, distribution, metabolism and excretion studies. Therefore, the bone marrow will have been exposed to SYN545974 in the in vivo rat bone marrow chromosome aberration study.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 20180608 CLH submission pydiflumetofen - non-confidential.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20180608 CLH submission pydiflumetofen - confidential.zip

Dossier Submitter's Response

The additional rat bone marrow chromosome aberration assay submitted during the peer review process under Regulation 1107/2009 has been included and assessed by the DS in the revised DAR. The DS concluded that pydiflumetofen did not induce chromosome aberrations in the bone marrow cells of male rats treated up to 2000 mg/kg. In addition, the DS is of opinion that on the basis of systemic exposure values available in toxicokinetic studies, the bone marrow have been sufficiently exposed: pydiflumetofen was detected in significant amount in blood (Cmax= 612 mg/ml (rat)) up to 24h.

However, the DS was questioning in the DAR on the need of a confirmatory *in vivo* assay on pydiflumetofen. In the opinion of the DS, the more adequate test should be an *in vivo* COMET assay to be performed on an organ from the GI tract and liver. Indeed, this additional test would allow to definitely exclude the possibility of a genotoxic mode of action for the liver tumors and to ensure of the absence of genotoxicity on a local tissue exposed upstream liver metabolism (e.i. gastrointestinal tract). The result of this study could also cover the genotoxicity of the major metabolite of pydiflumetofen, 2,4,6 TCP for which only very limited data are currently available *in vivo*.

Discussion regarding the issue regarding the need of a confirmatory in vivo assay will take place during the EU expert discussion (PRAS) in September 2018.

RAC's response

The additional rat bone marrow chromosome aberration assay has also been assessed by RAC. RAC concluded that pydiflumetofen did not induce chromosome aberrations in the bone marrow cells of male rats treated with up to 2000 mg/kg.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
08.06.2018	Switzerland	Syngenta Crop Protection AG	Company-Manufacturer	7

Comment received

A prenatal developmental toxicity study in the rabbit was conducted on Pydiflumetofen (SYN545974) in 2013, using the New Zealand White rabbit, available in the dossier. There was an increased incidence of costal cartilage when compared to control.

In order to contextualise the incidence of this variant, a further assessment of the adversity of the occurrence of costal cartilage has been included in the attached report (Manton J, 2018). Following a comparison of the incidence with the HCD ranges from 54 studies, where higher incidences have been observed on numerous occasions, this variation is considered to be spontaneous in origin and is observed in the New Zealand White rabbit irrespective of animal supplier. Subsequently, these incidences of interruption of the costal cartilage of the rib are not indicative of an adverse effect of Pydiflumetofen, as the incidence is within the spontaneous background data ranges in the New Zealand White rabbit from the respective supplier between 2007 to 2017.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment 20180608 CLH submission pydiflumetofen - non-confidential.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 20180608 CLH submission pydiflumetofen - confidential.zip

Dossier Submitter's Response

During the peer-review process under Regulation 1107/2009, the applicant submitted historical control data for the costal cartilage variant from 54 rabbit prenatal developmental studies performed by the conducted laboratory. These data have been assessed by the DS and included in the revised DAR. Taking into account a limitation to a frame time of +/- five years with respect to the completion date of the rabbit developmental study with pydiflumetofen (42 studies performed between 2010 to 2017), the increase at the highest dose of 500 mg/kg/d is within the spontaneous background data range for foetus incidence (8% vs 9.4%) and slight above the range for litter incidences (47.6% vs 44.5%). At 100 mg/kg bw/d, the increase in both litter and foetus incidences is above the HCD ranges (see Table 6.6.2-21a in the revised DAR).

RAC's response

This is noted by RAC. The possibility of a relationship to treatment cannot be excluded. However, costal cartilage variant can be considered spontaneous in origin in NZW rabbits. In addition, this finding is not defined as a malformation, but rather, as variations in cartilage development that do not impact on normal growth or function. Attention is drawn to the absence of other associated changes in any rib parameters and the absence of a dose relationship. There is no retardation of foetal growth and development associated with pydiflumetofen at ≥ 100 mg/kg bw.

Date	Country	Organisation	Type of Organisation	Comment number
08.06.2018	Denmark		MemberState	8

Comment received

In the DAR, a number of malformations was described which the DEPA considers may be treatment-related.
In both the rat and rabbit developmental studies summarised in the DAR, cleft palate/palatine and/or malformed palate was observed at the highest dose tested (rat main study at 100 mg/kg bw/d; rabbit preliminary study at 1000 mg/kg bw/day).
In the rat developmental study (Report No. BFI0118), palate malformations were observed in two fetuses from one litter at the highest dose of 100 mg/kg bw/day. This appears to be within the HCD from the control laboratory (Sequani) for litter frequency, however, the fetus frequency of 0.67% was outside HCD of 0.4%. Additional HCD was is given in the DAR in Table 6.6.2-18, and the reported malformations of the palate seen in the study with pydiflumetofen appear to be outside these additional HCDs.
It is to be noted that it is concluded in the DAR that the NOAEL for both maternal and developmental effects is set at the highest dose tested (100 mg/kg bw/day) and from this conclusion it may be argued that sufficiently high doses have not been tested in the rat developmental study. A transient effect on bw gain was seen in high dose females compared with controls over the first four days according to the DAR, however, the size of this effect was not reported. In a preliminary study in rats (Report No. BFI0031), dose levels of 100, 200, 500 and 1000 mg/kg/day, was tested and concluded to be well tolerated and a dose level of 1000 mg/kg/day was considered a suitable high dose level for administration in a subsequent developmental toxicity main study (no fetal malformations were reported in the 5-6 dams/group). It was argued by the applicant that exposure/dose proportionality was demonstrated to be between 5 and 100 mg/kg/day for females, and therefore 100 mg/kg/day was considered to be an adequate highest dose. Even though a linear proportionality may not be found above 100 mg/kg bw/day, a dose-dependent transient effect on bw gain was seen in the preliminary rat developmental study and it is the opinion of the DEPA that a higher dose that would achieve toxicity as defined in the OECD guideline should have been used. Developmental toxicity in rats may therefore not be fully assessed in the dossier.
In the preliminary rabbit developmental study (Report No. BFI0046), one fetus from one out of five dams had malformed palate at the highest dose of 1000 mg/kg bw/day, and one fetus from one out of nine dams had cheilognathopalatoschisis at the dose of 250 mg/kg bw/day; no major fetal abnormalities were reported from the nine dams given the intermediate dose of 500 mg/kg bw/day nor from the additional high dose group with 8 dams. A clear dosis response was therefore not observed, however, it should be kept in mind that the AUC was only slightly increased with increased oral dosing (AUC increase by only 1.2 and 4.2 fold following a dose increase of 10 (dose of 100 mg/kg/day) and 50 fold (dose of 500 mg/kg/day), respectively). In the main rabbit developmental study (Report No. BFI0116), no malformations of the palate was reported (dose regimen: 0, 10, 100 and 500 mg/kg bw/day). However, a low frequency of a number of severe malformations were reported in foetuses of the pydiflumetofen-treated dams (e.g skeletal, neural arches, diaphragmatic hernia).
It is noted as well that a skeletal abnormality/variation in costal cartilage was observed in both rats and rabbits (Rat: There were also significant ($p<0.05$) increases in the number of litters with fetuses showing the minor abnormality, absent costal cartilage at 100 mg/kg/day, just within the HCD given. Rabbit: A marginally increased incidence of cartilage variant (one or more costal cartilage interrupted (rib)) was observed in the groups given 100 mg/kg/day or 500 mg/kg/day compared with control. The absence of available

historical control data leads difficult the interpretation of this findings.)

DEPA considers that these various developmental findings may be considered treatment-related and may be relevant for a classification for reproductive toxicity.

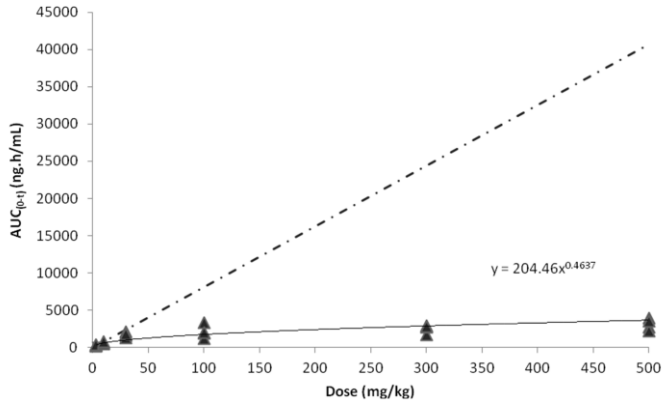
Dossier Submitter's Response

- **RAT DEVELOPMENTAL STUDIES**

Maternal effects and selected doses

According to DK, developmental toxicity in rats may not be fully assessed in the dossier taking into account that a dose achieving toxicity has not been tested in the main study (highest dose tested in the main study was 100 mg/kg/d). Indeed, in the preliminary prenatal developmental study in rat, a statistically significant reduction of body weight gain for females given 500 mg/kg/d (-97%) and a body weight loss (-3.7g) for females given 1000 mg/kg /d were observed between day 6 to day 7 of gestation. However, slight maternal toxicity has been also observed in the main developmental study at the highest tested dose: a statistical significant reduction of body weight gain was seen between the first days of dosage (days 6 to 10) at the highest tested dose of 100 mg/kg/d (maximum decrease of 90% between days 6 to 7; see additional information reported in Table 6.6.2-5 of the revised DAR). Based on this effect, a NOAEL of 30 mg/kg/day for maternel toxicity is now proposed by the DS in the revised DAR.
Anyway, the DS agrees that the doses selected by the applicant could have been higher than 100 mg/kg/day in the main study to be sure to properly assess the hazard according to the OECD guideline. However it should also be taken into consideration that PK data are available in female rat following oral administration of pydiflumetofen and these data have shown that the total systemic exposure (measured by AUC) stops to increase linearly with the dose above 100 mg/kg/d. Indeed, based on PK studies performed in female rat (Punler and Harris (2014); K-CA 5.1.1/06 report in the DAR Table 6.1.1-50 and figure 6.1.1-3), the AUC following daily oral administration for 7 days of pydiflumetofen was increased by 8 fold between the doses of 3 mg/kg/d and 100 mg/kg/d. Above 100 mg/kg/d dosage, the total systemic increase becomes clearly non-linear with only an increase by 1.3 fold when the dose increases by 3 (from 100 to 300 mg/kg/d) and by 1.5 fold when the dose increases by 5 (from 100 to 500 mg/kg/d).

Relationship between AUC(0-t) and dose in female rats following daily oral administration of pydiflumetofen for 7 days (Figure 6.1.1-3 of the DAR):



- **RABBIT DEVELOPMENTAL STUDY**

According to DK, a low frequency of a number of severe malformations were reported in foetuses of the pydiflumetofen-treated dams (e.g skeletal, neural arches, diaphragmatic hernia) in the main rabbit developmental study.

Diaphragmatic hernia:

During the peer review process, the applicant submitted additional HCD regarding diaphragmatic hernias (46 studies performed by the conducting laboratory between 2010 to 2017).The increase incidence of diaphragmatic hernia observed in one foetus at 500 mg/kg/d (1/154 (0.6%)) is well within the range of the HCD (0-1.6% (liver diaphragmatic hernia); 0-1.3% (stomach diaphragmatic hernia). The DS is of opinion that this finding can be considered as incidental and not treatment related.

Fresh visceral examination: Diaphragmatic hernia (Table 6.6.2-22 of the revised DAR)

Observations	**Dose levels (mg/kg bw/day)**				**HCD Sequani from the conducting laboratory**[#] Mean % (range)
	0	**10**	**100**	**500**	N = 36 studies (2010-2017)
No. of foetuses (F)	*163*	*142*	*132*	*154*	*3277*
No. litters (L)	*22*	*18*	*19*	*21*	*385*
Liver: diaphragmatic hernia	F: 0 (0%)	F: 0 (0%)	F: 0 (0%)	**F: 1 (0.6%)** **L: 1 (4.8%)**	F: 0.18% **(0-1.6%)** L: 1.6% **(0-14.3%)**
Stomach: diaphragmatic hernia	F: 0 (0%)	F: 0 (0%)	F: 0 (0%)	**F: 1 (0.6%)** **L: 1 (4.8%)**	F: 0.06% **(0-1.3%)** L: 0.5% **(0-11%)**

Skeletal and neural arches malformations:

Malformations related to skeletal and neural arches were observed in 2 foetus at 100 mg/kg/day:

- one foetus presented a spina bifida with associated vertebral malformations (bifid 7th lumbar to 4th sacral neural arches, severely fused 6th to 8th caudal centra) and
- the other foetus presented multiple malformations and in particular related to the skeleton (malformed and discontinuous lumbar cord; malrotated hindlimbs; filamentous tail, centrally placed kidneys, undescended testes; 10 thoracic vertebrae, 10 pair of ribs; 10th centra absent; 10th neural arches malformed&fused, absent lumbar sacral&caudal vertebrae)

Skeletal and neural archs malformations (severely fused 4th to 5th thoracic centra, 4th & 5th right ribs arising from the same neural archs) were also observed in one foetus at 500 mg/kg/d. However, all these skeletal malformations are within the HCD provided by the conducting laboratory (13 studies performed between 2009 to 2013)

External and fresh examination: other major abnormalities

Observations	**Dose levels (mg/kg bw/day)**				**HCD Sequani from the conducting laboratory**[#] Mean % (range)	
	0	**10**	**100**	**500**	N = 13 studies (2009-2013)	
Spina bifida	F: 0 (0%)	F: 0 (0%)	**F: 1 (0.7%)** **L: 1 (5.3%)**	F: 0 (0%)	F: 0.03% (0-0.7%) L: 0.41 (0-5.6%)	
Severely fused 4th to 5th thoracic centra	F: 0 (0%)	F: 0 (0%)	F: 0 (0%)	F: 1 (0.6%) L: 1 (4.8%)	Thoracic centra: one or more: major fusion	F: 0.11% (0-0.7%) L: 0.97% (0-5.3%)
Bifid 7th lumbar to 4th sacral neural archs	F: 0 (0%)	F: 0 (0%)	**F: 1 (0.7%)** **L: 1 (5.3%)**	F: 0 (0%)	lumbar neural arch: one or more :bifid	F: 0.03% (0-0.7%) L: 0.48% (0-5.6%)
4th & 5th right ribs arising from the same neural arch	F: 0 (0%)	F: 0 (0%)	F: 0 (0%)	**F: 1 (0.6%)** **L: 1 (4.8%)**	Ribs: one or more: arising from same neural arch	F: 0.05% (0-0.7%) L: 0.48% (0-5.3%)
Absent lumbar sacral & caudal vertebrae	F: 0 (0%)	F: 0 (0%)	**F: 1 (0.7%)** **L: 1 (5.3%)**	F: 0 (0%)	Sacral centra: absent Caudal vertebrae: absent	F: 0.06% (0-0.7%) L: 0.48 (0-5.3%) F: 0.06% (0-0.6%) L: 0.48 (0-4.8%)

Skeletal variation in costal cartilage

During the peer-review process under Regulation 1107/2009, the applicant submitted historical control data for the costal cartilage variant from 54 rabbit prenatal developmental studies performed by the conducted laboratory. These data have assessed by the DS and included in the revised DAR. Taking into account a limitation to a frame time of +/- five years with respect to the completion date of the rabbit developmental study with pydiflumetofen (42 studies performed between 2010 to 2017), the increase at the highest dose of 500 mg/kg/d is within the spontaneous background data range for foetus incidence (8% vs 9.4%) and slight above the range for litter incidences (47.6% vs 44.5%). At 100 mg/kg bw/d, the increase in both litter and foetus incidences is above the HCD ranges (see Table 6.6.2-21a in the revised DAR).

Skeletal examination: rib: costal cartilage variant (Table 6.6.2-21a of the revised DAR)

Observations	Dose levels (mg/kg bw/day)				HCD Sequani from the conducting laboratory[#] Mean % (range)
	0	**10**	**100**	**500**	N = 42 studies (2010-2017)
No. of foetuses (F)	*163*	*142*	*132*	*154*	*732*
No. litters (L)	*22*	*18*	*19*	*21*	*6101*
Rib: one or more: costal cartilage interrupted (variant)	F: 4.4% L: 27.3%	F: 5% L: 33.3%	**F: 14%** **L: 63%***	**F: 8%** **L: 47.6%***	F: 0.9% **(0-9.4%)** L: 5.7% **(0-44.5%)**

- **CLEFT PALATE/ MALFORMED PALATE** (rat and rabbit developmental studies)

Rat:
In the preliminary developmental rat study, no major fetal abnormalities were observed up to 1000 mg/kg bw/d.
In the main developmental rat study at 100 mg/kg bw/d (high dose), 2 fetuses in one litter presented malformations of the oral cavity (cleft palate/ malformated palate, cleft palatine) associated with malformations of the head (inter-parietals, parietals, frontals and nasals), exencephaly and open eye. However, this increase incidence is within the historical control range provided by the conducting laboratory for litter incidence in cleft palate/ malformed palate in studies performed between 2008 and 2012.

Rabbit:
In the preliminary developmental rabbit study, one foetus presented oral cavity and jaw abnormalities associated with cyclopia and proboscis at 1000 mg/kg bw/d (high dose) and one foetus presented cheilognathopalatoschisis (cleft lip, jaw and palate) at 250 mg/kg bw/d. However, in the main developmental rabbit study, no malformation of oral cavity/ cleft palate was observed up to 500 mg/kg bw.d.

The DS is of opinion that these palate malformations seen in developmental studies (rat and rabbit) can be considered as incidental and not treatment-related (multi-malformed foetuses, only one litter concerned, incidences within the HCD).

RAC's response

The DS has covered the response in detail. There is little further that RAC can add to this comment. In the rabbit a considerable number of malformed foetuses were recorded across the doses from control to 1000 mg/kg bw. No particular dose or treatment-related pattern was apparent with the exception of a rib variant (one or more costal cartilage interrupted) which was elevated from 100 mg/kg bw/day. Costal cartilage variant can be considered spontaneous in origin in NZW rabbits. In addition, this finding is not defined as a malformation, but rather as variations in cartilage development and do not impact normal growth or function. Classification is not proposed on the basis of this finding.

The foetal malformations and variations seen in the rat main study lack a dose-response relationship and statistical significance when compared with the controls, and were not

apparent in the previous preliminary dose-range finding study at significantly higher doses of pydiflumetofen (100, 500 and 1000 mg/kg bw/d). This demonstrates a distinct lack of dose concordance; no major foetal abnormalities were observed up to 1000 mg/kg bw/d in the preliminary rat study. These findings are not considered treatment related by RAC.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
29.05.2018	Germany		MemberState	9

Comment received

Page 129 ff table 57 summary of relevant information on acute aquatic toxicity:
Relating the studies for algae and aquatic plants of Soucy, 2014 with the marine diatom Skeletonema costatum and Soucy, 2015 with the freshwater blue-green algae Anabaena flos-aquae. These study results should be considered as supplementary information from our point of view, because both studies does not fulfill validity criteria of coefficient of variation for mean daily growth rate in the controls below 35%.

Page 142, point 2.9.2.3.2 chronic toxicity to aquatic invertebrates:
The lowest reported NOEC was for the water flea Daphnia magna (NOEC = 0.042 mg/L) instead of the value given for mysid shrimp Americamysis bahia (NOEC= 0.037mg/L).

Dossier Submitter's Response

For the first comment about Anabaena flos-aquae and Skeletonema, although the mean daily growth rate CV in control is above the validitiy criteria, all other validity criteria were fulfilled and particularly the overall average specific growth rate CV is below the validity criteria of 7 %. These results may be due to the colonial behaviour of these algae leading to high variability section-by- section couting but more homogenous global results during the whole test period.
The test was therefore considered valid and relevant, and was not challenged during the peer review of the active substance. It can also be noted that those studies are not key studies for acute and long-term environmental hazards as algae are not most sensitive aquatic organisms. No impact on overall conclusion for classification.
For the second comment, it was undoubtfully due to a misprint: The NOEC for Americamysis bahia is 0.076mg/L.

RAC's response

Thank you for your comment.

RAC notes the clarification provided by the Dossier Submitter regarding the validity of the study with the marine diatom *Skeletonema costatum* and with the freshwater blue-green algae *Anabaena flos-aquae*. RAC agrees with the respond of Dossier Submitter that those studies are not the key studies for acute and long-term environmental hazards as algae are not the most sensitive aquatic organisms. Therefore, those studies would not affect acute and chronic classification of pydiflumetofen. RAC proposes Aquatic Acute 1 based on EC_{50} value of 0.12 mg/L for freshwater amphipod *Hyalella azteca* and Aquatic Chronic 1 based on NOEC value of 0.025 mg/L for fish *Pimephales promelas*.

The editorial mistakes are noted.

RAC noticed that the year of the cited reference for freshwater blue-green algae *Anabaena flos-aquae* is not correct, it should be 2013.

Date	Country	Organisation	Type of Organisation	Comment number
08.06.2018	Belgium		MemberState	10
Comment received				
Based on the results reported in the CLH dossier and the comparison with the CLP criteria, the proposed environmental classification of Aquatic Acute 1, H400 ; Aquatic Chronic 1, H410 and M acute and M chronic equal to 1, seems warranted. Despite the use of the new template , it is difficult to make an independent assessment of the environmental hazards as no info is given on the GLP status of the studies, their reliability, validity, possible deviations from the study protocol, … Fate and behaviour : not always clear which guideline and test method is used, sometimes references are not mentioned. For more details, reference is made to the volumes of the DAR, which are not annexed to the CLH report and thus not consultable. Some editorial or/and minor comments : Chronic aquatic toxicity invertebrates: in table 59 a 28 day NOEC (survival, reproduction, growth) of 0.076 mg/l is reported for Americamysis bahia, (idem in table 93), while in the description above table 93 it is mentioned that the lowest reported NOEC for the mysid shrimp Americamysis bahia is 0.37 mg/L. Please correct.				
Dossier Submitter's Response				
Regarding fate and behaviour, guideline and test method used were indicated for the key study relative to ready biodegradability. Complete information for all other studies is available in the DAR (Vol. 3 B8). Please note that the DAR was submitted to ECHA with the CLH Report and is also publicly available on the EFSA website. Summary of the relevant key studies for acute and long-term environmental hazards were added to the CLH-Report. Thank you, the table was amended. The correct NOEC is 0.076 mg/L.				
RAC's response				
Thank you for your comments. RAC notes the support for the proposed environmental classification. The editorial mistakes are noted.				

Date	Country	Organisation	Type of Organisation	Comment number
08.06.2018	Denmark		MemberState	11
Comment received				
bioaccumulation has been addressed for the active substance but no mention is made of the water metabolites SYN548261 (photolysis, max 7.3 % AR), NOAA449410 (photolysis, max 5.8 % AR), SYN545547 (aerobic, max 12,3% AR in total system). The metabolites are not measured in the bioconcentration study, no Kow value via experimental or QSAR approach is available for the metabolites and no discussion is made concerning their bioaccumulative potential. It should be highlighted that this needs to be assessed especially for the aerobic metabolite SYN545547 which is present in relatively high amounts in the sediment.				

Dossier Submitter's Response
PYDIFLUMETOFEN (SYN545974) has a low potential for bioaccumulation and **is not rapidly degradable**. This last criteria (not rapidly degradable), associated with the value of the NOEC drives the chronic classification and corresponding M-Factor proposal for environmental hazards. Based on this, the comment has no impact on harmonised classification proposal for environmental hazards.
RAC's response
Thank you for your comment. RAC agrees with the response provided by Dossier Submitter.

Date	Country	Organisation	Type of Organisation	Comment number
19.04.2018	United Kingdom		MemberState	12

Comment received

We agree with the Aquatic Acute 1 (M-factor 1) classification on the basis of the Hyalella azteca 48-h EC50 of 0.12 mg/l.

We agree that the substance should be considered not rapidly degradable.

The chronic classification proposal of Aquatic Chronic 1 (M-factor 1) cites a 32-d NOEC (survival, mean length and mean dry weight) for Pimephales promelas of 0.025 mg/l as the basis of the classification. As statistically derived effect endpoints (EC10 / EC20) for weight and length are available, these should be used in preference to the NOEC. While a NOAEC is presented for survival, it is unclear if such EC10/EC20 endpoints are available for survival – please can you confirm?

We note that P. promelas was not the most acutely sensitive fish species and that the surrogate approach should be considered using the 96-h LC50 for Oncorhynchus mykiss of 0.18 mg/l. This would result in Aquatic Chronic 1 (M-factor 1).

A chronic endpoint is presented for Hyaella azteca (42-d NOEC 7.6 mg/kg). While study details are not presented to consider its reliability, table 93 notes that the endpoint is based on spiked sediment. On this basis, it is unclear if the endpoint is suitable for hazard classification. Applying the surrogate approach using the 48-h EC50 of 0.12 mg/l would result in Aquatic Chronic 1 (M-factor 1).

Overall, we agree with the Aquatic Chronic 1 (M factor 1) classification but consider this should be based on the surrogate approach for the most acutely sensitive endpoints as valid chronic endpoints for these species are not available.

Dossier Submitter's Response

FR confirms that EC10 was calculated for *P. promelas* but only for "Total length" and "Dry weight". The NOEC of 0.025 mg a.s./L was based on the "Live, Normal Larvae at Hatch" and was considered valid and relevant during the peer review process of the active substance. FR considered that *P. promelas* and *Oncorhynchus mykiss* have acute sensitivity in the same order of magnitude and therefore chronic data on *P. promelas* was considered relevant for classification. Moreover, despite UK has some questions concerning chronic fish study, it can be noted that chronic classification of Aquatic Chronic 1 associated with M factor 1 would also be concluded based on available chronic study on *Daphnia*. FR considered that *Daphnia* and *Hyaella azteca* have acute sensitivity in the

same order of magnitude and therefore chronic data on *daphnia* was considered relevant for classification.

In the end, UK agrees with FR classification proposal.

RAC's response

Thank you for your comments.

RAC agrees with the Dossier submitter and commenting Member State that the substance should be considered not rapidly degradable.

RAC notes the support for the proposed acute environmental hazard classification of pydiflumetofen. Furthermore, RAC notes that the commenting Member State agreed with the proposed chronic environmental classification but suggested that the surrogate approach should be considered for fish and invertebrates.

In line with the current CLP Guidance (Version 5.0, July 2017), if available, the preference is given to the chronic toxicity data over acute toxicity data for defining the long-term hazard category. However, when assessing the adequacy there may be some cases (such as data poor substances) where the chronic data do not represent the species that is considered the most sensitive in available short-term tests. In such cases the classification should be based on the data (acute or chronic) that gives the most strict classification and M-factor.
The criteria for classification of a substance into the categories Chronic 1 to 3 follow a tiered approach where the first step is to see if available information on chronic toxicity merits long-term (chronic) hazard classification. In absence of adequate chronic toxicity data, the subsequent step is to combine two types of information, i.e. acute aquatic toxicity data and environmental fate data (degradability and bioaccumulation data) (see Figure 4.1.1).

RAC is of the opinion that adequate chronic toxicity data are available for all three trophic levels, although the data for the most acutely sensitive fish species and acutely sensitive invertebrate species is not represented. The lowest chronic toxicity value corresponds to a test with fish *Pimephales promelas* with determined 32-d NOEC of 0.025 mg/L. The substance therefore meets the criteria for classification with Aquatic Chronic 1 (H410). As $0.01 < \text{NOEC} \leq 0.1$ mg/L, and the substance is not rapidly degradable, the M-factor is 1. A chronic test with the most acutely sensitive fish species in the data set (*Oncorhynchus mykiss*, 96-h LC_{50} = 0.18 mg/L) is not available whereas an an acute endpoint is available for *P. promelas* (96-h LC_{50} = 0.35 mg/L). RAC agrees with DS that the sensitivity of this two species is in the same order of magnitude. Therefore it is appropriate to consider chronic data on *P. promelas* relevant for chronic classification. RAC notes that chronic classification of Aquatic Chronic 1 associated with M-factor of 1 would be reached also based on surrogate data for fish.

During the Public consultation on Member state (see comment 14) pointed out that the NOEC for mysid shrimp *Americamysis bahia* (28-d NOEC = 0.076 mg/L) should have been selected as the most critical endpoint for aquatic invertebrates instead of NOEC for *Daphnia magna* (selected by Dossier Submitter). RAC agrees with commenting MS (see response to comment 14). RAC notes that the chronic toxicity value for *D. magna* (21-d NOEC = 0.042 mg/L, EC_{10} = 0.085 mg/L) and *Americamysis bahia* (28-d NOEC of 0.076 mg/L) are in the same concentration range as for fish *P. promelas* (32-d NOEC = 0.025 mg/L). RAC agrees with Dossier Submitter and commenting Member State that the freshwater amphipod *Hyalella azteca* is the most acutely sensitive invertebrate species.

The chronic toxicity data are not available for this species. *Hyalella azteca* (48-h LC_{50} = 0.12 mg/L), *Daphnia magna* (48-h LC_{50} = 0.42 mg/L) and *Americamysis bahia* (96-h LC_{50} = 0.16 mg/L) have acute sensitivity in the same order of magnitude. On this basis RAC is of the opinion that it is appropriate to consider the chronic data for *Americamysis bahia* relevant for classification. Classification based on chronic toxicity data for *A. bahia* would result in Aquatic Chronic 1 with M-factor 1. The same conclusion would be drawn based on surrogate data for invertebrate.
Overall, the same conclusion on classification is reached based on adequate chronic toxicity data or surrogate data for fish and invertebrates.
In conclusion, on the basis of the available data, RAC considers that pydiflumetofen should be classified as Aquatic Chronic 1 with M-factor of 1 based on 32-d NOEC of 0.025 mg/L for *Pimephales promelas* and lack of rapid degradability. This is consistent with the conclusion of the Dossier Submitter.

Date	Country	Organisation	Type of Organisation	Comment number
07.06.2018	France		MemberState	13

Comment received

FI CA supports the conclusion that pydiflumetofen is neither rapidly degradable nor potentially bioaccumulative. The acute aquatic toxicity based on the lowest of the reliable toxicity values is between 0.1 and 1 mg/L. There are adequate information on long-term toxicity available for all trophic levels. The chronic aquatic toxicity based on the lowest of the reliable toxicity values is between 0.01 and 0.1 mg/L.

Based on classification criteria FI CA supports the proposed environmental classification Aquatic Acute 1, H400 with M-factor of 1 and Aquatic Chronic 1, H410 with M-factor of 1 for pydiflumetofen.

Dossier Submitter's Response

Thank you for your comment.

RAC's response

Thank you for your comment. RAC notes the support for the proposed environmental classification.

Date	Country	Organisation	Type of Organisation	Comment number
04.06.2018	Netherlands		MemberState	14

Comment received

Agreed with comments

Proposed comments
NL agrees with the proposed classification and M-factors for acute and chronic aquatic toxicity. However we do not agree with the selected NOECs for aquatic invertebrates and aquatic plants presented in Table 60. The CLP guidance indicates that when EC10 values are available these preferred over NOECs. This applies in cases where EC10s are available for the same endpoint. The selected NOEC for Daphnia magna covers the endpoint survival, reproduction and growth. For these endpoints, EC10 values are available separately. Therefore the EC10 of 0.085 mg/L for reproduction should have been selected for Daphnia magna. This value is however higher than the NOEC for Americamysis bahia of 0.076 mg/L for survival, reproduction and growth. For this study, EC10 values could

not be derived and therefore the NOEC for Americamysis bahia is the most critical chronic endpoint for aquatic invertebrates. The same applies for the selected NOEC for Naviculla pelliculosa of 0.89 mg/L for growth. For growth also an EC10 of 0.97 mg/L is available in this study which should have been selected as the most critical endpoint for aquatic plants.
Dossier Submitter's Response
Thank you for your comment. The endpoints are updated in the CLH-Report and EC10 added. It does not change the initially proposed classification.
RAC's response
Thank you for your comment. RAC notes the support for the proposed environmental classification. According to current CLP Guidance (Version 5.0, July 2017), if available preference is given to the EC_{10} value over the NOEC value. RAC agrees with commenting MS that the EC_{10} value of 0.085 mg/L over the NOEC of 0.042 mg/L for *Daphnia magna* shoul be selected as the lowest value for this species. RAC also agrees that NOEC of 0.076 mg/L for *Americamysis bahia* should be selected as the most critical chronic endpoint for aquatic invertebrates. RAC agrees with commenting MS that the EC_{10} value of 0.97 mg/L over the NOEC of 0.89 mg/L for *Naviculla pelliculosa* shoul be selected as the most critical endpoint for algae and aquatic plants. RAC is of the opinion that selected most critical chronic endpoint for aquatic invertebrates and algae/aquatic plants do not affect proposed chronic classification. RAC consideres that pydiflumetofen should be classified as Aquatic Chronic 1 based on 32-d NOEC of 0.025 mg/L for fish *Pimephales promelas*. This is consistent with the conclusion of the Dossier Submitter.

PUBLIC ATTACHMENTS
1. 20180608 CLH submission pydiflumetofen - non-confidential.zip [Please refer to comment No. 1, 6, 7]

CONFIDENTIAL ATTACHMENTS
1. 20180608 CLH submission pydiflumetofen - confidential.zip [Please refer to comment No. 1, 6, 7]