Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

4-{[(6-chloropyridin-3-yl)methyl](2,2-difluoroethyl) amino}furan-2(5*H*)-one; flupyradifurone

EC Number: -

CAS Number: 951659-40-8

CLH-O-0000001412-86-228/F

Adopted

14 September 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 4-[(6-CHLORO-3-PYRIDYLMETHYL)(2,2-DIFLUOROETHYL)AMINO]FURAN-2(5*H*)-ONE; FLUPYRADIFURONE

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: 4-[(6-chloro-3-pyridylmethyl)(2,2-difluoroethyl)amino]furan-2(5*H*)-one; flupyradifurone
EC number: -
CAS number: 951659-40-8
Dossier submitter: The Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
27.10.2017	Germany	Bayer AG - CropScience Division	Company-Manufacturer	1
Comment received				
Comments have been provided under the reproductive toxicity sections together with accompanying documents under the attachment section to provide evidence that the limited effects on reproductive parameters are clearly associated with reduced maternal body weight. In absence of other effects both on the reproductive parameters and on fetal development, Flupyradifurone is not meeting the criteria for classification for reproductive toxicity. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Flupyradifurone_position_papers.zip				
Dossier Submitter's Response				
Thank you for your comment. See our response to comment 3				
RAC's response				
Thank you for your comment. A more detailed answer to your comments is provided in the specific section on reproductive toxicity.				

Date	Country	Organisation	Type of Organisation	Comment number
27.10.2017	Germany		MemberState	2
Comment received				
DE agrees with the proposed classification as Repr. 2, H361; Acute Tox. 4 H302 and STOT RE 2, H 373. We agree with the proposal of classification for environmental hazards as Aquatic acute 1 (H400) and Aquatic chronic 1 (H410) and the acute/chronic M-factor of				

10. Concerning explosive properties, the reason for no classification "Data lacking" would be more appropriate (see specific comment and attached document). ECHA note – An attachment was submitted with the comment above. Refer to public attachment attachment-de-comment-physical-hazards-flupyradifurone.pdf
Dossier Submitter's Response
Thank you for your comment. Unfortunately we cannot alter the CLH report after public consultation. However, we will consider your comment for future CLH proposals.
RAC's response
Thank you for your comment. Flupyradifurone was investigated under a test battery which cannot be directly related to the CLP regulatory text. However, the results proved negative in three relevant key areas: behaviour to heat, shock and friction. RAC considers that there are sufficient data to conclude that flupyradifurone should not be classified for Explosive properties under the CLP Regulation although the exothermic decomposition energy of the substance is 895 J/g between 270° C and 355 °C. With regard to the classification for Repr. 2, RAC is of the opinion that there is not enough evidence from the two-generation study to classify as a reproductive toxicant. Based on the three in vitro endocrine disruption assays, it can neither be confirmed nor excluded that flupyradifurone is an endocrine disruptor. The other studies provided in the CLH-report (a one-generation dose range-finding study, three developmental toxicity studies, one developmental neurotoxicity study) do not support a classification for reprotoxicity.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
27.10.2017	Germany	Bayer AG - CropScience Division	Company-Manufacturer	3
Comment received				
In the rat two-generation study with Flupyradifurone the following effects were observed: reduced number of estrous cycles of the F1 females at the high dose and reduced numbers of implantation sites and pups. According to the rapporteur, it was unclear whether the observed effects on the second generation (F1) females are secondary to the reduced body weights. As a result, the Rapporteur considered that the criteria for category 2 are met and that Flupyradifurone (BYI 02960) needs to be classified as Reproductive toxicant Cat. 2, H361." Therefore, Bayer CropScience re-evaluated the estrous cycle data using the method of Goldman (M-544703-01-1) and ran additional statistical analyses using body weight as a covariate to clarify the relationship between effects on body weight and number of estrous cycles , reduced number of implantation sites or litter size (M-544703-01-1 and M-604609-01-1). Results confirm that the marginal variations of these parameters observed at the high dose do well correlate with reduced body weight. The outcome of this re-analysis does not show significant difference among the control and treated groups, including the high dose group of F1 females. Overall, the available data show limited effects on reproductive parameters clearly associated with reduced maternal body weight and no other effects both on the reproductive parameters and on fetal development. Therefore, Flupyradifurone is not meeting the criteria for classification for reproductive toxicity. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Flupyradifurone_position_papers.zip				
Dossier Submitter's Response				
Thank you for your response.				

Estrous cycle number

To support your view about the insignificance of estrous cycle results in the 2-generation toxicity study, an alternative approach is proposed to re-calculate the number of estrous cycles, based on a method of Goldman et al. (2007). In this reanalysis of the individual estrous cycles, no significant difference was found between the mean number of cycles of the exposed groups and the controls. This is in contrast with the original results, which show a decrease in estrous cycles in the high dose group of the F1 generation. Originally the study was performed and analyzed according to the method described in OECD 416, which is the standard method for a 2-generation study. There is no particular reason to doubt the validity of the results of the original study. The position paper also does not provide strong scientific argumentation why the method of Goldman et al. should be preferred over the standard OECD 416 method. In addition, the daily estrous cycle status shows a strong increase in females with irregular cycling from 6 out of 30 animals in the F1 control group to 15 out of 30 animals in the F1 high dose group. This confirms the estrous cycle effects as originally observed in the 2-generation study. Hence, we see no reason to adapt the results presented in the CLH proposal based on your alternative analysis.
Furthermore, it is argued that the reduction in the number of estrous cycles is causally related to the reduction in body weight gain. We agree that the lower body weight and decrease in number of estrous cycles occur together. However, this observation on its own does not prove a causal relationship, as both effects may also be caused by the exposure to FDF independently. As we argued in the discussion of the CLH report, it is doubtful whether the reduction in body weight after exposure to FDF is severe enough to cause an increase in estrous cycle length. This is illustrated by the study by Carney et al. (2004), which was also mentioned in the position paper and Chapin et al. (1993). In the study by Carney et al. (2004), a decrease in the number of estrous cycles of the F1 generation was observed after 50% feed restriction (30-43% lower body weight post weaning), but not after 30% feed restriction (6-19% lower body weight post weaning) (see tables 3 and 8 of Carney et al. (2004)). The body weight of the F1 females of the high dose group in the 2-gen study was reduced by 15.9% at day 70, which is more comparable to the body weight reduction after 30% than 50% feed restriction in the Carney study. In conclusion, this study does not provide evidence that shows the reduction in estrous cycles in the high dose F1 females is related to the reduction in body weight gain, in fact it may even support the argument on the contrary. In accordance with observations from Chapin (1993) and Carney et al. (2004), the weight loss in the parental and F1 females would be below the level expected to have an influence on the observed reproductive effects in the 2-generation study. Please view the table below for an overview and comparison of the findings from these studies.
We would further like to note that the individual animal data in your position paper (Figure 1) suggest a relation between body weight and the number of estrous cycles for the F1 control females with the number of estrous cycles reducing with lower weights. However, as there were no control F1 females with body weights comparable to the F1 high dose animals, a direct comparison is not possible.

Table: Summary of Reproductive effects in relation to body weight

reference	Body weight reduction parental animals (%)	Body weight reduction F1 (%)	Reproductive effects observed (yes/no)
2-generation study (Milius 2011) with flupyradifurone	up to 21%	17-12% (PND0-PND21)	yes
Carney et al (2004), feed restriction	up to 20%	up to 21% (up to PND 21)	no
	17-32%	12- 47% (PND0 - 21)	yes
Chapin et al (1993),	Up to 30%		no

Feed restriction		
	30-40%	yes

Implantation sites and number of pups
Both the number of implantation sites and the number of pups were significantly reduced in the high-dose group of the F1 generation. In the position paper, it was again argued that these effects were caused by the reduction in body weight of the dams.
As discussed in the CLH report, there is some evidence in the literature that a reduction in body weight may lead to a reduction in implants. However, the evidence is not very strong, especially when the reduction in body weight is relatively small (<30%). In addition, the study of Carney et al. (2004) found a slight decrease in litter sizes in the 50% feed restricted group, all values were well within historical control ranges. They reported no effect on litter size in the 30% feed restricted group.

In the position paper, a linear regression analysis was used to substantiate the claim that the reduction in the number of implantation sites was related to the reduction in body weight. However, this regression analysis was performed after grouping the data in 'high' and 'low' body weight groups. This results in a gross simplification of the data and is not a valid statistical analysis as it artificially removes all variation. For example, the point with the highest mean body weight (P0 control, ≥median) has a mean number of implants of 11.7, but a range from 6-17, which is a variation of approximately 50%. With the method used, this variation is not accounted for. In addition, the calculations seem to contain an error as for the F1 high dose group, the average weight of the animals above the median (199.7 g) was below the median (203.5 g).
The resulting R_2's only give some indication of the difference between the P0 and F1 generation, as this is the only source of variation included in the regression analysis (Figure 3 of the position paper). These R_2's cannot be used to draw any conclusions on the relationship between body weight and number of implantation sites. Not to mention that this combination of generations is also not acceptable, as two separate groups are combined without any justification. The difference in the slope between the controls and the high dose animals can also be explained by assuming that there is another factor such as an effect of the substance via another mechanism than body weight involved.
To perform a valid linear regression analysis, one would have to determine the best fit through the original data (Figure 2 in the position paper) for all four groups. Although we did not perform this analysis, considering the large spread in the data points, it is highly likely that the slope of this line will be close to zero, with a weak correlation. Hence, it cannot be concluded that there is a correlation between body weight and number of implantation sites, let alone a causal relationship, based on the regression analysis included in the position paper.
Overall the comparisons between body weight reductions as a result from feed restriction and the body weight reduction in the 2-generation study suggest the reduction in weight gain and body weight likely have limited impact on the reproductive effects observed in the the 2-generation study.
Please also note the number of estrous cycles/length and implantations/litter size of the P/F1 generations were not the only positive reproductive endpoints. For example, there was also a delay in preputial separation and vaginal patency (F1 generation).

It is argued that flupyradifurone is not an endocrine disruptor by comparing the effects of flupyradifurone to the endocrine disruptors methoxychlor and vinclozolinIt should be noted that even if no endocrine-mediated mode of action is established, this does not prove that the reproductive effects were caused by a reduction in maternal body weight. It is very well possible for a substance to have adverse effects on reproductive parameters without being an endocrine-disruptor. It is also good to notice that also methoxyclor and vinclozolin caused a reduction in body weight (not quantified).

Moreover, the analysis presented in the discussion uses only two substances for the comparison, which is insufficient to draw general conclusions. It is not possible to conclude whether or not FDF has endocrine-disrupting properties solely on the discussion provided in part 1 of the position paper.

Part 2 – Summary of in vitro studies

It is unclear why the response in the third *in vitro* test was deemed equivocal rather than positive in the position paper, as the EPA Guideline (890.1550) commends the following interpretation of the results:
"A chemical is judged to be positive if the fold induction is statistically different from the solvent controls following concentrations that fall within the increasing or decreasing portion of the dose-response curve. Statistically significant increases in fold-induction indicate the chemical is an inducer of one or more enzymes in the steroid synthesis pathway. Statistically significant decreases in fold-induction indicate the chemical is an inhibitor of one or more enzymes in the steroid synthesis pathway. Statistically significant differences at concentrations that do not follow a dose-response curve may be due to random effects; such results are considered to be equivocal."

The decreases in the production of testosterone and estradiol were observed at the highest concentration, thus should be considered dose-dependent and categorized as a positive response.

In conclusion, three *in vitro* endocrine disruption screening assays were performed of which the estrogen receptor transactivation assay was negative, the androgen receptor binding assay was equivocal and the steroidogenesis assay was positive (showed inhibition of both testosterone and estradiol synthesis). The effects observed in these studies occurred only at relatively high concentrations, but were reproducible in repeat runs. Based on these results, it cannot be confirmed nor excluded that FDF is an endocrine disruptor.
The purpose of these *in vitro* studies was to determine whether FDF possesses endocrine disrupting properties that may explain the effects observed in the 2-generation study. Again, it is not possible to conclude on this mode of action, as the results of two of the *in vitro* studies were equivocal. In addition, even if these tests were negative no metabolic capacity was present in the tested systems. As flupyradifurone is intensively metabolized and these metabolites have not been tested, an endocrine disruptive mechanism cannot be excluded.

Conclusion

In the position paper, it was argued that the effects of FDF in the F1 group of the 2-generation study were solely related to the reduction in maternal body weight. Three new endocrine disruption screening studies were performed to determine whether the effects were related to possible endocrine disruptive properties of FDF. The outcome of one of these studies was positive, one was equivocal and one was negative, hence no definite conclusion can be drawn on the outcome of these studies.

For reasons discussed earlier, we do not agree there is clear evidence that either the reductions in the number of estrous cycles, implantation sites, or number of pups is caused by the reduction in maternal body weight.
The *in vitro* studies show that some endocrine disruptive potential cannot be excluded. And even if these studies would have been negative, it is still very well possible for a substance to have adverse effects on reproductive parameters without being an endocrine-disruptor. Thus, the lack of strong evidence for an endocrine-mediated mode of action does not prove that the reproductive effects were caused by a reduction in maternal body weight.

In conclusion, we remain of the opinion that the effects observed in the 2-generation study should be considered relevant and warrant classification for Repr. 2 H361 (suspected of being a reproductive toxicant). We would like to repeat this classification proposal is in accordance to the CLP regulation since there are signs of reproductive toxicity, but clear evidence is lacking to be able to classify for Repr 1A or 1B.

Added references:

RAC's response

Thank you for your comment and the re-evaluation of the estrous cycle data using the method of Goldman. However, RAC supports the DS´s opinion that as the original study was performed and analysed according to OECD TG 416, there is no reason to consider the Goldman et al. (2007) approach more appropriate in analysing the study than the approach described in the guideline. It is clear that reduced body weight results in an increase in oestrous length and in a reduction in the number of developing eggs but, as pointed out by the DS, but it is not clear whether all the observed effects on the F1 females are secondary to the reduced body weight (e.g. delay in preputial separation and vaginal patency; reduced brain, thymus and speen weights). This leads to some uncertainty in the evaluation of this endpoint.

The bodyweight may have a significant influence over implantation site numbers, as indicated by the overall control values (range: 9.6 to 12.2) and the correlation (according to Table 2, Regulatory Toxicology Position Paper by Bayer CropScience, January 14, 2016). It is noted that the influence of body weight (and probably of body weight gain during gestation) on implantation sites differed between controls and treated animals (slope of the linear regression line through the control data was 0.061 vs. 0.019, respectively). Therefore, a direct relation to the treatment on implantation sites (primarily in F1 generation) in addition to a secondary influence of the body weight and body weight gain cannot be excluded.

However, in summary, although there are some uncertainties (e.g. whether the body weight decrease is the only reason for the decreased reproductive success, whether there is an endocrine MoA which effects the length of the estrous cycles in the F1 high dosed females and influences the number of implantation sites), RAC does not consider the observed effects in the F1 generation to be severe enough to warrant a classification for flupyradifurone as Repr. 2.

Date	Country	Organisation	Type of Organisation	Comment number
27.10.2017	Germany		MemberState	4

Comment received

Proposal for classification as Repr. 2, H361 is supported. Slight, but statistically significant decrease in the litter size was observed in high-dose F2 pups (-9 %). This decrease was associated with reduced BW gain (-19 %) during gestation and a decreased number of implantation sites (-17 %) in the high-dose F1 females. In addition, significant delay in preputial separation and a slight non-statistical delay in vaginal patency were observed in F1 females. While there is some uncertainty whether the effects in F1 females are due to reduced body weights, reproductive toxicity cannot be excluded. Moreover, (equivocal) indications of endocrine activity are observed in vitro. Data on developmental toxicity in rats indicates no need for specific classification since the observed incomplete ossifications were not clearly dose-dependent and mostly within historical control data.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment attachment-de-comment-physical-hazards-flupyradifurone.pdf
Dossier Submitter's Response
Thank you for your comment and considerations.
RAC's response
Thank you for your comments. Although there are some uncertainties (e.g. whether the body weight decrease is the only reason for the decreased reproductive success, whether there is an endocrine MoA which effects the length of the estrous cycles in the F1 high dosed females and influences the number of implantation sites) RAC does not consider the observed effects in the F1 generation to be severe enough to warrant a classification for flupyradifurone as Repr. 2.

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	Belgium		MemberState	5
Comment received				
BECA supports the dossier submitter's proposal and agrees to classify Flupyradifurone as Repro. 2 (H361). Indeed, main effects were reported in a two-generation study (Milius et al., 2011) where an increase in the oestrus cycle length (4, 4.1, 4.4 and 4.4 at 0, 100, 500 and 1800 ppm, respectively), a decrease in the number of oestrus cycle (3.5, 3.3, 3.3 and 2.9* at 0, 100, 500 and 1800 ppm, respectively) and in the median number of implantation sites (12, 11, 11 and 10** at 0, 100, 500 and 1800 ppm, respectively) were seen in the F1 generation. Mean litter size at day 0 was also decreased (11, 11, 10.5 and 10 pups per litter at 0, 100, 500 and 1800 ppm, respectively). As these effects appeared only in the F1 generation, it is not clear if the concern may be related to a fertility or developmental concern. Therefore, we agree with the dossier submitter and we support the given justification to not mention the specification. Furthermore, a significant delay in preputial separation and a slight delay in vaginal patency was observed in F1 pups, increasing the concern about reproductive toxicity of the compound. Finally, some neuro-developmental effects were noted in a developmental neurotoxicity study (Gilmore et al., 2012) where a slight increase in motor and locomotor activity were noted in males and an increase in auditory startle habituation was recorded in females at 102 mg/kg bw/d. ECHA note – An attachment was submitted with the comment above. Refer to public attachment flupyradifurone STOT RE .docx				
Dossier Submitter's Response				
Thank you for your comment and considerations.				
RAC's response				
Thank you for your comment. RAC notes that there are some uncertainties related to the reasons for effects in the F1 generation. However, RAC does not consider the observed effects in the F1 generation to be severe enough to warrant a classification for flupyradifurone as Repr. 2. The effects on increased motor/locomotor activity and auditory startle habituation were noted at the same dose level in offspring but they are considered by RAC to be secondary to general toxicity. However, since the pesticidal mode of action of flupyradifurone is based on nicotinic acetylcholine receptor (nAChR) agonist property and no MoA studies have been provided, it cannot be excluded that neurotoxic effects observed in offspring are related to the above properties. Besides, a significant decrease in brain weight was consistently observed in offspring (on day 21) in the two-generation study. In the developmental				

neurotoxicity study, the high dosed males showed a decrease of brain weight of 5 % on PND 75. However, since the decrease in brain weight cannot be related to the effects on nAChR and since there is no indication of a MoA, RAC does not consider these effects sufficient to support a classification for reproductive toxicity for flupyradifurone.

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	France		MemberState	6

Comment received

Page 197, classification proposal for Repr. 2, H361 (without specification f or d) is supported. However other effects may also be taken into account for classification purposes.
Indeed, along with reduced number of estrous cycles of the F1 females (unclear whether this should be considered an effect on fertility or development), the following effects may also be considered for reproductive classification even if effect on body weights were observed at the same dose levels:
- reduced number of implantation sites in top dose F1 females in the 2-generation study
- Statistically significant delay of balano- preputial separation observed in the 2-generation study. Indeed, BW at preputial separation was not affected, therefore a direct effect cannot be ruled out.
- Statistically significant decrease of brain weight consistently observed in offspring in the 1-generation range finding study, in the 2-generation study and in the developmental neurotoxicity study. Indeed, brain weight is relatively insensitive to body weight change. According to OPPTS 870.6300 (1998), "A change in brain weight is considered to be a biologically significant effect. This is true regardless of changes in body weight, because brain weight is generally protected during undernutrition or weight loss, unlike many other organs or tissues." Furthermore in the DNT, increased motor/locomotor activity and startle habituation were noted at the same dose level in offspring. Taking also into account the pesticidal mode of action of flupyradifurone based on nicotinic acetylcholine receptor (nAChR) agonist property, the neurotoxic effects observed in offspring provide evidence of increased quantitative susceptibility of developing organisms.

Dossier Submitter's Response

Thank you for your considerations and support.

RAC's response

Thank you for your comment. With regard to the observed effects in the F1 females, please see RAC´s answer to comment no 3. With regard to the observed neurotoxic effects in the developmental neurotoxicity study, please note RAC´s answer to comment no 5.

Date	Country	Organisation	Type of Organisation	Comment number
29.10.2017	United Kingdom		Individual	7

Comment received

The hazard classification of Repro Category 2 for flupyradifurone has been proposed by the Netherlands Rapporteur, based upon the findings in the high dose group (1800 ppm) F1 females in a two generation rat study of a slight reduction in the number of oestrous cycles during the 21 days prior to mating and a reduced mean number of F2 implantation sites. Similar effects were not observed in the F0 females. It is TCI's opinion that these observations do not meet the criteria for R2 classification for the following reasons:
In the original study report the number of oestrous cycles for F1 females at 1800 ppm

was statistically reduced compared with the concurrent controls (2.9 v. 3.5; $p<0.05$). The high dose group value was within the historical control range of 2.5 – 4.0 cycles for F0 females and was just below the range of 3.0 – 3.9 cycles for F1 females. Despite the slight reduction in cycle number there was no difference in mean cycle length. In a position paper submitted by Bayer CropScience, oestrous cycle numbers, using the original data recordings, have been recalculated according to the method of Goldman et al. (2007), which explains in depth how to evaluate rat estrous cycles in toxicology studies. After re-evaluation, although there remained a slight reduction in cycle numbers (3.3 v. 3.7), the difference was not statistically significant. In both cases, the slightly lower cycle number in the high dose F1 females appeared to result from a small number of females in which di-oestrus, denoted by the presence of leucocytes, was marginally extended between oestrus, which was denoted by the presence of cornified cells. However, despite the slight change in oestrous cycle length, mating performance, pregnancy rate and gestation length of the F1 high dose group females, and survival of F2 concepti either in utero or post-natally during the lactation period were not affected. Goldman et al (2007) stated that "exposure to environmental compounds may alternatively induce irregular or moderately extended ovarian cycles. These latter changes should be interpreted with caution and not judged adverse without a comprehensive consideration of additional relevant endpoints in a weight-of-evidence approach."
Body weights of F1 females were depressed from post-natal day 1 and at week 10, when vaginal smearing began, mean body weight was 16% lower than that of the controls but food consumption was unaffected. Carney et al. (2004) published the results of a study in which food restriction was used as a tool to manipulate body weight. Their results indicated that a reduction in food consumption of F0 females by 50% during gestation and for the F1 offspring throughout the F1 generation resulted in F1 animals with body weights that were 12% - 47% lower than those of the controls. In their study, puberty of F1 females was delayed and oestrous cycle length was increased, which resulted in a lower number of cycles in a given period. For females that received 1800 ppm of flupyradifurone, mean body weight was reduced by 16% and these females also showed a slight delay in the onset of puberty. It was not unexpected, therefore, considering the results of Carney et al. (2004) that these females also had a lower number of oestrous cycles. In the position paper submitted by Bayer CropScience, the data for oestrous cycles for the control and high dose group F1 females have been plotted graphically with respect to body weight and a clear relationship between lower numbers of oestrous cycles and lower bodyweight of females was demonstrated. The effect on oestrous cycles, therefore, is considered to be a consequence of the reduced female body weight.
The total number of implantation sites in F1 females at 1800 ppm was marginally reduced compared with the concurrent controls (mean: 9.7 v. 11.3, ns; median: 10.0 v. 12.0, $p<0.01$) and there was a consequent slight reduction in the viable litter size at birth (mean: 9.2 v. 10.8, ns; median: 10.0 v. 11.0, $p<0.05$). Nevertheless, the mean number of implantations in the high dose group was within the historical control ranges of 8.8 – 12.6 for F0 females and 9.7 – 10.8 for F1 females. The subsequent viability of F2 pups to weaning was unaffected by treatment. Again, when the number of implantations was plotted against female body weight, a clear relationship between lower numbers of implantations and lower body weights was apparent,
In order to investigate whether an endocrine mediated mechanism might have played a part in the effects on oestrous cycles and the number of implantations, three in vitro endocrine disruption screening assays were performed with flupyradifurone, namely binding to estrogen or androgen receptors and interference with steroidogenesis. In the oestrogen receptor transactivation assay there was no indication that flupyradifurone was an agonist of the human estrogen receptor alpha. For the androgen binding receptor assay the results at high concentrations were equivocal whilst the steroidogenesis assay was considered positive by the Rapporteur but equivocal by Bayer CropScience. Thus no consistent endocrine mode of action was demonstrated. In their review of the in vitro

assays that comprise part of the EPA Tier 1 screening programme for endocrine disrupters, LeBaron et al. (2014) commented that the fact that a substance may interact with a hormone system, or result in hormonal perturbations, does not suggest that when the substance is used it will cause adverse effects in humans or wildlife species. Results of Tier 1 screening tests should be considered together with other scientifically relevant information in a weight of evidence approach.
In summary, the high dose level of 1800 ppm was associated with a slight reduction in the number of F1 oestrous cycles, but no adverse effects were recorded upon mating performance, pregnancy rate or gestation length. There was also a slight reduction in the number of F2 implantation sites but this had no impact upon subsequent offspring survival. For both of these findings a clear association with reduced maternal bodyweight was demonstrated. In vitro endocrine assays showed no consistent results. On a weight of evidence basis, therefore, taking into account the absence of any downstream consequences on reproductive performance, it is considered that flupyradifurone should not be classified as a reproductive toxicant.
References
Carney E.W., Zablotny C.L., Marty M.S., Crissman J.W., Anderson P., Woolhiser.M., Holsapple M. (2004): The Effects of Feed Restriction during in Utero and Postnatal Development in Rats. Toxicological Sciences 82 pp. 237-249
Goldman J.M., Murr A.S., Cooper R.L.. (2007): The rodent estrous cycle: characterization of vaginal cytology and its utility in toxicological studies.
Birth Defects Res B Dev Reprod Toxicol. 80(2) pp.84-97.
LeBaron M.J., Coady K.K., O'Connor J.C., Nabb D.J., Markell L.K., Snajdr S., Marty M.S. (2014): Key learnings from performance of the U.S. EPA endocrine disruptor screening programme (EDSP) Ties 1 in vitro assays.
Birth Defects Res, B 101 pp. 23-42

Dossier Submitter's Response

Thank you for your considerations. Please see our response to comment 3.
We do like to add a single note in response here. It seems there are different interpretations on how the study by Carney et al. (2004) relates to the 2-generation study by Milius et al. (2011). For example, you state that the 16% reduction in body weight in the 2-generation study can be compared to the 50% feed restriction group corresponding to 12-47% body weight reduction in the F1 in Carney et al. (2004). However the 12-47% in Carney et al. refers to the weight at PND 0-PND21 where the lower corresponds to the first post natal days (PND0). This cannot be compared directly to the <16% weight reduction in F1 reported in the 2-generation study refers to the pre-mating body weight. The body weight reduction during lactation ranged between 12-17% compared to the control, which corresponds more to the up to 21% weight reduction during PND0-21 reported by Carney et al (2004), where no reproductive effects were observed.

RAC's response

Thank you for your comment. With regard to the observed effects in the F1 females, please see RAC´s answer to comment no 3.

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2017	Denmark		MemberState	8

Comment received

Agrees with RMS that a classification as Repro cat 2 is justified based on results of the 2-generation study. It has not been shown that the effects on estrus cycle and number of implantations and pups in the F1 generation can be explained as secondary effects to the reported reduced body weight (16%) in in the pre-mating period. Furthermore, the epididymis sperm count is decreased in both the P-generation and the F1-generation in

the 2-gen study by ≥ 10 %, although not statistically significant. This is also observed in testes (-12%) in the P-generation (but was not seen in F1). Dose-response is not possible to assess because sperm count were not determined in the low and mid dose groups, but the effect on sperm number may be treatment related and considered for classification for fertility.
Dossier Submitter's Response
Thank you for your comment and considerations. The reduction in epididymis sperm count is limited and we believe insufficient to conclude on effects for fertility. Notably, in Study 3 section STOT RE a reduction in epididymis weight (-18% relative to BW) is observed in mice at and above 50 mg/kg bw/day. However this effect was not supported by histological findings and within historical control range. There seems to be an effect, but such a limited reduction in sperm count/epidydimis weight is not strong enough evidence to conclude on possible fertility effects. However, these results may be considered by the RAC together with other reprotoxic endpoint results in a weight of evidence approach to accept or decline the proposal for Repr 2 H361.
RAC's response
Thank you for your comment. According to RAC, the effects on the sperm count in the two-generation reproductive toxicity study are not considered to be adverse. However, RAC agrees with the DS that in the subacute 28-day study in mice some effects are observed on the absolute and relative epididymis weights, starting at a concentration of 50 mg/kg bw/day. Since these effects neither show a clear dose-response relationship nor are they associated with relevant histological findings, RAC supports the DS´s view that the evidence was not strong enough to conclude on possible fertility effects. Besides, the epididymides weights are in the range of the historical control data from the same laboratory using mice from the same supplier administered with the same diet.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
27.10.2017	Germany		MemberState	9
Comment received				
Classification proposal as Acute Tox. 4, H302 is supported. ECHA note – An attachment was submitted with the comment above. Refer to public attachment attachment-de-comment-physical-hazards-flupyradifurone.pdf				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	France		MemberState	10
Comment received				
Page 75, FR agrees with classification proposal for Acute Tox. 4, H302.				
Dossier Submitter's Response				
Noted				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	Spain		MemberState	11
Comment received				
The Spanish CA agrees with the NL CLP Competent Authorities that, flupyradifurone should be classified as Acute Tox 4 (H302), based on mortality at 2000 mg/kg bw but not at 300 mg/kg bw/day in an acute oral toxicity test according to the acute toxic class method (OECD 423).				
Dossier Submitter's Response				
Noted				
RAC's response				
Thank you for your comment. Category 4 in general applies for doses ≥ 300 mg and ≤ 2 000 mg/kg bw/day. The LD_{50} for oral acute toxicity might be somewhere in between.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
27.10.2017	Germany		MemberState	12
Comment received				
STOT RE 2 (muscle), H 373 is supported; 28-day dog study: According to 4.8.2 (p.117) "minimal to slight myofiber atrophy/degeneration and weight loss were observed in a 28-day dog study at 118/131 mg/kg bw/day", but no mention of myofiber atropy/degeneration is made in the study 4 (p.93) summary under 4.7.1.1.1. Observed muscle effects were consistent in the dog studies, and so severe in the 90-day study that the high doses were reduced. The issue if "muscle" is in fact the target organ or an effect secondary to the weight loss should be further clarified. Necrosis and the presence of inflammatory cells around the affected myofiber might be indicative of direct tissue damage. ECHA note – An attachment was submitted with the comment above. Refer to public attachment attachment-de-comment-physical-hazards-flupyradifurone.pdf				
Dossier Submitter's Response				
Thank you for your comment and considerations. In the 90-day dog study, reduced body weight (11-13%) was observed at the same dose level as myofibre atrophy. In the 1-year dog study, muscle toxicity was observed in the absence of weight reduction (reduced weight gain only observed in the first week in females). Since effects are seen in the 1-year study without significant body weight reduction, it is likely the muscle is not a secondary effect of body weight reduction or general toxicity.				
RAC's response				
Thank you for your comment. The lack of information about myofiber atrophy/degeneration in the 28-day dog study is noted. However, the effects in the **muscles** observed in the long-term dog studies are rather severe since atrophy and necrosis were observed in the 1-year dog study. In addition, these effects do not seem to be a secondary effect due to weight loss as in the 1-year dog study weight loss did not occur. Besides, in the 90 day study in dog, severe changes in clinical chemistry indicative of muscle toxicity (creatinine phosphokinase, alanine				

aminotransferase) supports that the muscles effects are sufficiently severe for classification.
RAC concludes that classification for STOT RE 2 is warranted as myofiber atrophy/degeneration (irreversible effect) was observed in both sexes at dose levels much lower than 100 mg/kg bw/day in a 90-day dog study, supported by the same findings in a 1-year dog study at 28.1/28.2 mg/kg bw/day (at slightly higher doses than the extrapolated CLP-Regulation value for STOT RE 2 which is ≤ 25 mg/kg bw/day). In addition, as no underlying mode of action is demonstrated, the relevance for humans cannot be excluded.

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	Belgium		MemberState	13

Comment received

BE CA welcomes this proposal for harmonized classification and labelling. We support a STOT RE 2 classification for flupyradifurone targeting muscle. However, BE CA believes that a category 2 classification is also required regarding the hepatotoxicity of flupyradifurone.
Indeed, liver has been broadly demonstrated to be the main target organ after repeated exposure to flupyradifurone. The various observations demonstrating the hepatotoxic potential of flupyradifurone include absolute and relative liver weight gain, clinical chemistry findings (decrease of total bilirubine and glucose concentration and increase of triglycerides, urea, creatinine, alanine aminotransferase and alanine phosphatase) and observations of enlarged liver, centrilobular hepatocellular hypertrophy and prominent lobulation. Finally, the hepatotoxicity of flupyradifurone has been observed in three different species (rat, mouse and dog).
The LOAEL's for liver toxicity of flupyradifurone are resumed in the following table :
ORAL EXP. 28 days study Ref. 90 days study Ref.
NOAEL (mg/kg bw/d) LOAEL (liver)
(mg/kg bw/d) NOAEL (mg/kg bw/d) LOAEL (liver)
(mg/kg bw/d)
rat 75 200 Capt (2007) 6 156 Odin-Feurtet (2009)
mouse 98 240 Blanck (2007) 81 407 Odin-Feurtet (2009)
dog (beagles) 62 131 Odin-Feurtet (2008) 12 33 Eigenberg (2010)
Equ. guidance values (STOT RE 2, oral, rat) ≤ 300 ≤ 100

The Annexe I : 3.9.2.9.8 of the guidance on the Application of the CLP Criteria also states that "The guidance values and ranges mentioned in paragraphs 3.9.2.9.6 and 3.9.2.9.7 are intented only for guidance purposes, i.e., to be used as a part of the weight of evidence approach, and to assist with decision about classification. They are not intended as strict demarcation values". Therefore, BE CA believes that the weight-of-evidence is in favor of a classification of flupyradifurone as presumed to have the potential to be harmful to human liver (STOT RE 2).
Although the effects may seem reversible, the effective dose level being in the range or below the equivalence guidance values for STOT RE 2 and the repetition of the same observations in different species should not be neglected and lead to a classification.
As a conclusion, BE CA support a STOT RE 2 classification (liver and muscles).

ECHA note – An attachment was submitted with the comment above. Refer to public attachment flupyradifurone STOT RE .docx

Dossier Submitter's Response

Thank you for your comment and opinion. We proposed to classify for STOT RE 2 muscle as muscle is the most sensitive endpoint. Although borderline, the effects observed in the

liver and related clinical chemistry findings were not considered sufficiently severe at doses below the guideline value to warrant inclusion of the liver as target organ.
The LOAEL proposed for liver toxicity on basis of glucose reduction in the 28 day rat study (Capt 2007) was in male rats only, while the liver weight was increased in females only. The effects on e.g. alanine aminotransferase in the 28-day mouse study (Blanck 2007) showed no clear dose-response relationship and the individual variability was high. The centrilobular glycogen accumulation in dogs is not considered clinically relevant/adverse. The LOAEL's proposed for liver effects in the 90-day studies (Odin-Feurtet 2009) for rats and mice fall outside the ranges for classification.
Moreover, as also noted in your comment, the effects observed seem reversible and more consistent with an adaptive response, rather than signs of marked organ dysfunction.

RAC's response

Thank you for the comment. Although increased absolute and relative liver weight, clinical chemistry findings as well as centrilobular or diffuse hepatocellular hypertrophy and prominent lobulation were observed in the liver in three different species (in rats and dogs at dose levels relevant for classification as STOT RE 2), RAC agrees with the DS and considers these effects rather as non-specific (adaptive) effects and not as indications of a marked organ dysfunction. The results of the two chronic toxicity/carcinogenicity studies in rats and mice provide further support that the effects in the liver might not be severe enough to consider the liver as a targed organ.

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	France		MemberState	14

Comment received

Page 118, FR agrees with classification proposal STOT RE Cat. 2 H373 (muscle) based on myofiber atrophy/degeneration consistently observed in the 28-day, 90-day and 1-year studies in dog. It should be noted that creatin phosphokinase is a marker of muscle injury (e.g.: rhabdomyolysis) and was increased from 400 ppm onwards in the 90-day study. Thyroid may also be considered as target organ for classification STOT RE since effects are observed in 90-day rat study from 30.2 mg/kg bw/day and in the 2-year study from 15.8 mg/kg bw/day (colloid alteration).

Dossier Submitter's Response

Thank you for your support and considerations. The effect observed in the 2-year study is outside the range for classification according to the CLP guideline. The effect in the 90-day study is indeed within the range required for classification. Notably, this effect was observed in males only and reversible without a clear relation to the treatment. In the absence of clear signs of thyroid toxicity within the range for classification in other repeated dose toxicity studies, we decided not to include the thyroid as specific target organ.

RAC's response

Thank you for the comment.
With regard to the effects observed in the thyroid, RAC agrees with the DS that these effects are not very consistent or sufficiently severe as to indicate the thyroid as a targed organ.

Date	Country	Organisation	Type of Organisation	Comment number
13.10.2017	Denmark		MemberState	15

Comment received

Agrees that STOT-RE Cat 2 (muscle) is justified. The picture is not so clear for the effect on blood, however. Considering the decrease in Hb >20 % at day 56, the dose cutoff

(corrected for an exposure duration of 56 days) is around 150 mg/kg and thus the effect is seen below the cutoff considered relevant for classification. The decrease in Hb was < 20% at the 90 day cutoff of 100 mg/kg bw/day (corrected for dose). However, there seemed to also be brown pigmentation (minimal) in liver Kupffer cells of females (which may be hemosiderin deposition) in high dose which could be taken into account regarding blood as a specific target organ. A decrease of MCV, RBC and Hct was also seen at the same doses. Were Heinz bodies/methemoglobin measured or were there just no effects on these? In conclusion, STOT-RE for effects on blood may be considered as well.

Dossier Submitter's Response

Thank you for your support and considerations. These effects were only observed in the 90-day dog study and the decrease in Hb was only (marginally) over 20% at day 56 (20.7% decrease). As Hb recovered to levels not significantly below the controls before the end of the study, animals may not have fully adapted to the exposure at this time point. For this reason, the entire study duration should be considered. The RBC and HgB levels were also reversible in the highest dose group. The pigmentation in liver kupffer cells was observed in high dose females only and it is not clear if this effect (as well as the HB level) is specific to blood toxicity. It may also be secondary to liver toxicity. In conclusion, we consider the effects on blood do not meet the criteria for classification.

RAC's response

Thank you for the comment. RAC agrees with the DS that the effects seen in blood are not severe enough to justify designating blood as a target organ.

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	Spain		MemberState	16

Comment received

Myofiber atrophy/degeneration were observed in a 90-day dog study at 33/41 and 102/107 mg/kg bw/day, the effects at the high dose (102/107 mg/kg bw/day) were considered so severe that the dose level for this group was reduced. Besides, in one year dog study at 28 mg/kg bw/day, degeneration was noted in skeletal muscle, protocol (gastrocnemius); and muscle, other (biceps femoris). Degeneration of the myofiber comprised of one or more of the following changes: atrophy, necrosis, and/or presence of inflammatory cells around the affected myofiber.

The Spanish CA considers that the observed effects in dogs were consistent, severe, and occurred below or around the guideline values. Therefore, we support the dossier submitter proposal to classify flupyradifurone as STOT RE Category 2 H373 (muscle).

Dossier Submitter's Response

Thank you for your support and comment.

RAC's response

Thank you for your comment.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
27.10.2017	Germany		MemberState	17

Comment received

p. 247, Table 152, chronic toxicity studies: The endpoint given for the study with C. riparius is not in line with the updated DAR (Dec. 2014) nor the LoEP. The given endpoint (4.1 µg a.s./L) is unclear.
p. 257, study 2 of 3 (aq. Invertebrates chronic): The study summary does not match the

endpoint given in Table 152 on page 247. According to the expert consultation and the final addendum to the DAR the 28-day NOEC is to be based on mean measured concentrations. The resulting NOEC is given in the DAR with 6.81 µg a.s./L (mm). The substance does not partition quickly to sediment. Likely the substance degrades relatively fast in water. The study summary appears not to match the endpoint given in table 152. p. 267, 5.4.4 Summary and discussion of aquatic toxicity: The chronic endpoint given for C. riparius is in line with the endpoint given in the study summary, but is not in line with the endpoint given for the same study in Table 152. In the DAR (Version Dec. 2014) and in the final LoEP the endpoint is given as NOEC = 0.00681 mg a.s/L (mm).

ECHA note – An attachment was submitted with the comment above. Refer to public attachment attachment-de-comment-physical-hazards-flupyradifurone.pdf

Dossier Submitter's Response

Thank you for your comments and for pointing out the inconsistencies. These will addressed below.

p. 247, Table 152, chronic toxicity studies: 0.010 mg a.s./L (nominal) should indeed be 0.00681 mg/L (mm) for *C. riparius* (as stated in the updated version of the DAR), conform "Table B.9.2.4.03 The chronic toxicity of BYI 02960 and BYI 02960 SL 200 to aquatic life." This was also put forward by the member state France (comment 19). The 4.1 µg a.s./L was based on the nominal concentration, corrected for the recovery of 41% as mentioned in the DAR. And indeed, as your comment on the summary and discussion on p. 267, here as well, the correct NOEC for *C. riparius*, chronic aquatic toxicity should be 0.00681 mg/L (mm) in stead of 0.010 mg a.s./L nominal (according to the updated DAR December 2014, V3-B9 part 1).

p. 257, study 2 of 3, the NOEC in the summary is 10 ug a.s./L and indeed, as mentioned above, this should have been the updated 0.00681 mg/L (mm). Furthermore, we note that the reference at page 248 in the table should be Bruns E. 2011g, similar to the summary at page 257 (and not 2011e). Finally, the comments regarding the behaviour of the substance in water and in sediment are noted (please see also response to comment 21). We would like to emphasis that toxicity tests with midge larvae (*C. riparius*) are valid for classification purposes of aquatic hazards and that this is study is considered reliable and supported with updated measured concentrations. The updated measured concentrations for the aquatic chronic key study with *Chironomus riparius* do not influence the classification, as the measured NOEC (geometric mean) is within the same M factor 10 range ($0.001 < NOEC \leq 0.01$ mg/L).

Considering ECHA's note, the Dossier Submitter cannot find any relevant information for the endpoint aquatic environment in the submitted attachement "attachment-de-comment-physical-hazards-flupyradifurone.pdf"

RAC's response

RAC noted the clarification and the updated information provided by the DS, according to the updated DAR December 2014, V3-B9 part 1. RAC agrees to base the chronic classification on the updated geometric mean measured concentrations for the aquatic key study with *Chironomus riparius*, although this does not influence the proposed classification.

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	Belgium		MemberState	18
Comment received				
Based on the results of the aquatic toxicity test on the most sensitive species (Chironomus riparius with 48hErC50=0.0617mg/l and 28dNOEC=0.010mg/l), the fact				

that the substance is not rapidly degradable it is justified to classify, following the classification criteria of regulation 1272/2008, as Aquatic Acute 1, H400 and Aquatic Chronic 1, H410. The substance does not meet the bioconcentration criterion (logKow=1.2 <4).

In view of the proposed classification and toxicity band for acute toxicity between 0.01mg/l and 0.1mg/l, an M-factor for acute toxicity of 10 should be assigned and an M-factor for chronic toxicity of 10 (not rapidly degradable substance and 0.001<NOEC≤0.01mg/l)

In conclusion : we agree with the proposed environmental classification.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment flupyradifurone STOT RE .docx

Dossier Submitter's Response

Thank you for your response and support.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	France		MemberState	19

Comment received

FR agrees with the general conclusion dealing with the classification for environmental hazard of the substance.
However, in accordance with the value reported in the conclusion on the peer review of the pesticide risk assessment of flupyradifurone (EFSA Journal 2015; 13(2) 4020), FR recommends the use of the mean measured NOEC value of 0.00681 mg/L.

Dossier Submitter's Response

Thank you for your comments and support. Indeed the NOEC for the chronic *C. riparius* study should be the updated value of 0.00681 mg/L (according to the updated DAR December 2014, V3-B9 part 1). This was also put forward by the member state Germany (comment 17).

RAC's response

RAC noted the clarification and the updated information provided by DS, according to the updated DAR December 2014, V3-B9 part 1. RAC agrees to base the chronic classification on the updated geometric mean measured concentrations for the aquatic key study with *Chironomus riparius*, although this does not influence the proposed classification.

Date	Country	Organisation	Type of Organisation	Comment number
30.10.2017	Finland		MemberState	20

Comment received

Toxicity tests with midge larvae (Chironomus riparius) are valid for classification purposes of aquatic hazards. According to chironomid studies, the acute toxicity EC50 value of flupyradifurone is between 10-100 µg/l and the chronic toxicity NOEC value is between 1-10 µg/l. However, the actual exposure could have been even lower since test endpoints were based on nominal concentrations eventhough the measured concentrations were being diluted during the chronic toxicity test. FI CA supports the conclusions that the

substance is neither rapidly degradable nor potentionally bioaccumulative.

Based on the available information and the classification criteria FI CA supports the proposed classification of Aquatic Acute 1 with M-factor of 10 and Aquatic Chronic 1 with M-factor of 10 for flupyradifurone.

Dossier Submitter's Response

Thank you for your response and support.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
20.10.2017	United Kingdom		MemberState	21

Comment received

We feel additional information is required to consider if the Bruns, 2011 chronic toxicity to C. riparius is valid for classification.
We note the test item declined over the 28 day study period and feel NOECs based on measured concentrations should be provided. This could include a geometric time-weighted mean method. In addition, clarification of whether the sediment phase was analysed for test item concentrations is required along with whether the test system was run in the dark. This information is relevant to understand test item losses and test organism exposure.

Dossier Submitter's Response

Thank you for your response and comments.
Indeed the member state is right that the correct NOEC for *C. riparius*, chronic aquatic toxicity should be 0.00681 mg/L (measured mean) in stead of 0.010 mg a.s./L nominal (according to the updated DAR December 2014, V3-B9 part 1).

Concentrations were measured of the overlying water and pore water, no samples of sediment are reported in the study results. There is also no mentioning of running the experiment in the dark in the DAR, so it is unlikely that the experiment was performed in the dark. Photolysis, as well as sorption, may contribute to dissipation of the compound and therefore indeed, measured concentrations should be used for classification. (As was also put forward by Germany, comment 17 and France, comment 19.)

The updated measured concentrations for the aquatic chronic key study with *Chironomus riparius* do not influence the classification, as the measured NOEC (geometric mean) is within the same M factor 10 range (0.001 < NOEC ≤ 0.01 mg/L).

Included here below, to clarify for your information, the updated table (with added measured concentrations, second column) from the DAR December 2014, V3-B9 part 1, p.68.

"Table B.9.2.2.1-03 Summary of biological results of 28-day chronic toxicity test with BYI 02960 technical on *Chironomus riparius*

nominal conc. (µg a.s./L)	geom. mean measured conc. (µg a.s./L)	emergence rate (%)	development rate (1/d)
solvent control	solvent control	90.0	0.058
1.25	0.679	87.5	0.058
2.5	1.25	92.5	0.057

5	2.25	83.8	0.058
10	6.81	88.8	0.059
20	15.4	52.5*	0.050*
40	29.8	0	0

* Statistically significant at 5% level

Conclusion
NOEC 6.81 µg a.s./L (based on mean measured concentrations).

Guidelines and limitations
The study was performed according to OECD 219 (2004) and is acceptable."

RAC's response

RAC noted the clarification and the updated information provided by DS, according to the updated Table B.9.2.2.1-03, from DAR December 2014, V3-B9 part 1. RAC agrees to base the chronic classification on the updated geometric mean measured concentrations for the aquatic key study with *Chironomus riparius*, although this does not influence the proposed classification.

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
27.10.2017	Germany		MemberState	22

Comment received

In section 3.1 of the CLH Report is stated that Flupyradifurone has no explosive properties as shown in the EEC A.14 study. No classification is proposed for physico-chemical properties under the CLP Regulation. However, in a Differential Scanning Calorimetry (DSC) measurement the substance showed an exothermal decomposition in the temperature range between 270 – 355 °C with a mean decomposition energy of 895 J/g. We criticise, that the comparison of EU test method A.14 with the CLP criteria has not been performed and that for validation on the CLP classification at least the following tests are required:
1. BAM Trauzl test (F.3) with initiation by a standard No. 8 detonator (see Appendix 1 in conjunction with Appendix 6, paragraph 3 of the UN RTDG, Manual of Tests and Criteria.
2. Based on the BAM Trauzl test results it should be decided if a further detonation test (UN gap test) would be required.
3. "Time/pressure test" (UN 2 (c) (i)) according to UN Test Series 2 in Part I of the Manual of Tests and Criteria.

As long as no evaluation based on UN Tests is available, the reason for no classification "Data lacking" would be more appropriate.

Justification:
Evaluation according to Figure 2.1.2 in Annex I of CLP Regulation for provisional acceptance of a substance, mixture or article in the class of explosives (Class 1 for transport)

For further details please see attached document.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment attachment-de-comment-physical-hazards-flupyradifurone.pdf

Dossier Submitter's Response

We agree that a conclusion stating no classification based on absence of data is appropriate.

RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
27.10.2017	Germany		MemberState	22

Comment received

In section 3.1 of the CLH Report is stated that Flupyradifurone has no explosive properties as shown in the EEC A.14 study. No classification is proposed for physico-chemical properties under the CLP Regulation. However, in a Differential Scanning Calorimetry (DSC) measurement the substance showed an exothermal decomposition in the temperature range between 270 – 355 °C with a mean decomposition energy of 895 J/g. We criticise, that the comparison of EU test method A.14 with the CLP criteria has not been performed and that for validation on the CLP classification at least the following tests are required:
1. BAM Trauzl test (F.3) with initiation by a standard No. 8 detonator (see Appendix 1 in conjunction with Appendix 6, paragraph 3 of the UN RTDG, Manual of Tests and Criteria.
2. Based on the BAM Trauzl test results it should be decided if a further detonation test (UN gap test) would be required.
3. "Time/pressure test" (UN 2 (c) (i)) according to UN Test Series 2 in Part I of the Manual of Tests and Criteria.

As long as no evaluation based on UN Tests is available, the reason for no classification "Data lacking" would be more appropriate.

Justification:
Evaluation according to Figure 2.1.2 in Annex I of CLP Regulation for provisional acceptance of a substance, mixture or article in the class of explosives (Class 1 for transport)

For further details please see attached document.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment attachment-de-comment-physical-hazards-flupyradifurone.pdf

Dossier Submitter's Response
We agree that a conclusion stating no classification based on absence of data is appropriate.
RAC's response
Noted.

PUBLIC ATTACHMENTS
1. flupyradifurone STOT RE .docx [Please refer to comment No. 5, 13, 18]
2. Flupyradifurone_position_papers.zip [Please refer to comment No. 1, 3]
3. attachment-de-comment-physical-hazards-flupyradifurone.pdf [Please refer to comment No. 2, 4, 9, 12, 17, 22