Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

pymetrozine (ISO); (E)-4,5-dihydro-6-methyl-4-(3-pyridylmethylene amino)-1,2,4-triazin-3(2H)-one

EC Number: -

CAS Number: 123312-89-0

CLH-O-0000001412-86-203/F

Adopted

9 March 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON PYMETROZINE (ISO); (E)-4,5-DIHYDRO-6-METHYL-4-(3-PYRIDYLMETHYLENEAMINO)-1,2,4-TRIAZIN-3(2H)-ONE

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: pymetrozine (ISO); (E)-4,5-dihydro-6-methyl-4-(3-pyridylmethyleneamino)-1,2,4-triazin-3(2H)-one
EC number: -
CAS number: 123312-89-0
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
29.08.2017	Netherlands		MemberState	1
Comment received				
With regard to the absence of information on the ECB discussion on this substance, some documents are available within our archive. These documents could be provided to ECHA and MSCA's upon request.				
Dossier Submitter's Response				
Thank you for the information.				
RAC's response				
Thank you very much. Noted.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
04.09.2017	Spain		MemberState	2
Comment received				
In mice treated for 18 month with pymetrozine, males at 2000 and 5000 ppm and females at 5000 ppm showed a significant higher incidence in liver carcinoma. The incidence of combined liver benign hepatoma and carcinoma was also significantly increased in males and females at 5000 ppm. In females it was also observed an increase in the incidence in lung adenoma and the combined incidence of lung adenoma and carcinoma at 2000 and 5000 ppm. Lung carcinoma were also increased at 100 and 2000 ppm in females, however the dose-response was less clear. In rats treated for 2 years with pymetrozine, males showed a significant increase in the incidence of malignant adrenal medullary tumours at the top dose of 3000 ppm (outside				

the historical control range of the laboratory), although the combined incidence of benign and malignant adrenal medullary tumours was not significantly increased. In females, benign liver hepatoma was significantly increased at 3000 ppm (outside the historical control range of the laboratory). There is hardly any data to elucidate the mechanism of action of the hepatic tumors observed in both species and the lung tumors in mouse and therefore it can´t be ruled out their relevance to humans. Therefore, the Spanish CA agree with the dossier submitter to keep the current classification of pymetrozine listed in Table 3.1 in CLP (category 2 (H351) for carcinogenic properties.
Dossier Submitter's Response
Thank you for the support.
RAC's response
Thank you very much. Noted.

Date	Country	Organisation	Type of Organisation	Comment number
04.09.2017	Belgium		MemberState	3
Comment received				
BE CA agrees that there is insufficient data to classify pymetrozine as a known human carcinogen (Category 1A), as there are no epidemiological studies available. However, the Category 2 doesn't seem appropriate to classify the carcinogenic potential of pymetrozine. First, an 18-month OECD guideline carcinogenicity study conducted on mice (0-10-100-2000 and 5000 ppm pymetrozine, 80 animals of each sex per dose level) demonstrated the carcinogenic potential of pymetrozine, mainly on the liver. Indeed, although there is no dose-response observed for the lung adenoma carcinoma (only observed in females, 32 % at 2000 ppm and 20 % at 5000 ppm), it seems that the resulting liver carcinoma are dose-related in mice, increasingly appearing with an incidence of 18 % at 2000 ppm and 46 % at 5000 ppm in males, and 8 % at 5000 ppm in females. Furthermore, the onset of liver carcinoma in males and of liver cell hypertrophy in both sexes at 2000 ppm seems to exclude a possible confounding effect of excessive toxicity, considering the mean body weight gains. In both sexes, there are also observations of liver carcinoma and hepatocarcinoma at 5000 ppm (68 % in males and 36 % in females). The apparition of malignant tumours in males at 2000 ppm and in both sexes at 5000 ppm constitute a first evidence of carcinogenicity supporting a Category 1B classification. Secondly, a 24-month OECD guideline carcinogenicity study has also been conducted on rats (0-10-100-1000-3000 ppm pymetrozine, 60 animals of each sex per dose level), showing benign hepatocellular adenoma in females (14 %) and benign granular cell tumour in males (4 %) at 3000 ppm. However, the study demonstrated a dose-related increase in liver hypertrophy in both sexes: 37 % and 61 % in males and 20 % and 67 % in females at 1000 and 3000 ppm, respectively. We cannot exclude that the observed liver hypertrophy is an early stage of a neoplasic development, especially knowing that a liver hypertrophy has also been observed in the 18-month mice study, as described above. Although BE CA acknowledges a low tumour incidence observed in rat, the apparition of neoplastic lesions in two different species (mouse and rat) strengthens a Category 1B classification.				

Finally, regarding the mode of action of pymetrozine, the weight-of-evidence shows a clear absence of genotoxic/mutagenic potential of pymetrozine. Although there is unfortunately no available test, some of the triazine containing metabolites are likely to be mutagenic compounds. In particular, CGA 215 525 and CGA 294 849 show a genotoxicity structural alert because of their aromatic amines. Moreover, it should be noted that the major target organ is the liver, main site of metabolization, which would make sense if the carcinogenic potential of pymetrozine is caused by one of its metabolites. BE CA therefore believes that the absence of genotoxic/mutagenic potential of pymetrozine should not be considered as a strong argument for a Cat. 2 classification. As a conclusion, the occurrence of tumors in two different species (rat and mouse), in two sexes (mouse) and in two types (liver benign hepatoma and/or carcinoma) are sufficient evidence of carcinogenicity. Hence, BE CA supports a Category 1B (H350) for pymetrozine carcinogenic toxicity.
Dossier Submitter's Response
Thank you for the comments. We agree that the available data set is not completely straightforward. When balancing the arguments increasing and decreasing the level of concern, we concluded that category 2 would be more appropriate. This uncertainty was one of the reasons to address the endpoint carcinogenicity in this dossier and to have it open for commenting.
RAC's response
Thank you very much. Noted.

Date	Country	Organisation	Type of Organisation	Comment number
04.09.2017	France		MemberState	4
Comment received				
Page 17: Classification proposal Carc. 2; H351 is supported.				
Dossier Submitter's Response				
Thank you for the support.				
RAC's response				
Thank you very much. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
29.08.2017	Netherlands		MemberState	5
Comment received				
Increases in the incidence of liver tumors were observed in mice and rats, of lung tumors in female mice (combined adenoma and carcinoma), and of adrenal medullary tumors in male rats. We agree that the relevance of the increase in adrenal medullary tumors in male rats is questionable. The liver was identified as a target organ of pymetrozine toxicity. The exact mechanism of tumor induction is not known, although increased proliferation seems to play a role. It is also unclear what caused the increase in lung tumors in female mice. What was the survival and cause of death in this study? According to the CLP criteria, positive evidence of carcinogenicity in two species is usually interpreted as sufficient evidence of carcinogenicity and reason to classify in Cat. 1B. However, deviations are possible if the studies have limitations that reduce the reliability of the outcome, of if there are reasons to doubt the relevance for humans. In this case, although the mechanism is unclear, there are no reasons to assume that the effects are not relevant to humans. The strengths and weaknesses of the studies are quoted as				

reason to propose Cat. 2, but it is not entirely clear which weaknesses are meant. Based on the current information, we consider a discussion of Cat. 1B is warranted. However, such a discussion would require additional study details and argumentations not currently provided in the CLH proposal.
Dossier Submitter's Response
Thank you for the comments. We agree that the available data set is not completely straightforward. When balancing the arguments increasing and decreasing the level of concern, we concluded that category 2 would be more appropriate. This uncertainty was one of the reasons to address the endpoint carcinogenicity in this dossier and to have it open for commenting. We are not clear, which additional study details would be missing from the CLH dossier, when also taking into account the annex to the CLH dossier (i.e., Final addendum to the renewal assessment report).
RAC's response
Thank you very much. Noted.

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2017	Denmark		MemberState	6
Comment received				
Danish EPA supports the proposed classification carc cat 2.				
Dossier Submitter's Response				
Thank you for the support.				
RAC's response				
Thank you very much. Noted.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
04.09.2017	Spain		MemberState	7
Comment received				
Fertility Histological findings in testes accompanied by other toxic effects were observed in several repeat-dose studies in dogs and rats, most pronounced at the highest dose groups. Histological indications for adverse effects on fertility (spermatogenesis) were reported in low incidences at dose levels inducing systemic toxicity. However, it seems that systemic effects of toxicity which were described in the study reports were not severe enough to render the observed histological findings in testes as non-specific and non-relevant findings for classification. No data are available to assess whether the testes effects in dogs might have an adverse impact on mating success. Although these findings could not be corroborated in the 2-year study in rats or in the multigeneration rat study, it has to be noted that doses used were slightly lower. Therefore, we agree with the German CLP CA that there is no reason to discount the testicular toxicity observed in rats and dogs as not being relevant for human health. Therefore, the Spanish CA considers necessary to classify pymetrozine for effects on fertility in category 2 (H361f).				

Developmental toxicity In rats, findings in offspring included displaced pubic bones (classified by the study director as malformation) and several foetuses with anomalies or variations in the top dose group. Increased incidence of variations (dumbbell shaped cervical vertebral centres) was also observed at the mid dose group. In rabbits, altered position of forelimb, fused sternebrae, reduced pubis, poor ossification of several bones and occurrence of 13th rib were observed in offspring in top and mid dose group. Besides, in a developmental neurotoxicity (DNT) study in rats, changes in brain morphometry were seen from the low dose offspring and pup mortality was observed in the mid dose group. Manifestations of developmental toxicity seen in developmental toxicity studies in rats and rabbits were accompanied by maternal toxicity. However, no information is available to confirm that the observed effects on offspring have to be regarded as secondary non-specific consequences of maternal toxicity. Additionally, findings in low and mid dose groups of the DNT study were not accompanied by maternal toxicity. The Spanish CA consider that the classification in Category 2 (H361d) proposed by the dossier submitter is appropriated. It is important to note that changes in the pelvis occurred in both species and the fact that, defects of this kind have not been recorded in historic controls in rabbits and only in low incidences in rats.
Dossier Submitter's Response
Thank you for the support.
RAC's response
Thank you very much. Noted.

Date	Country	Organisation	Type of Organisation	Comment number
04.09.2017	Belgium		MemberState	8
Comment received				
Classification in Category 2 (H361fd) is considered appropriate for pymetrozine as a suspected human reproductive toxicant. Although in the submitted multigeneration study no sufficient findings were reported, observations of histological findings in testes were observed in dogs and rats during 28-d studies, and it is assumed that these effects are not a secondary consequence of systemic toxicity. Considering the limitations of the multigeneration study in the rat, BE CA acknowledges that there are "some evidence" but not a "clear evidence" for pymetrozine human fertility and sexual function toxicity. Regarding pymetrozine adverse effects on development, the skeletal findings in teratogenicity studies showed alterations in rats and rabbits, associated with a maternal toxicity. However, some of the pubic alterations are considered as malformation and there is no information available to confirm that the observed developmental effects are secondary non-specific consequences of maternal toxicity. Consequently, BE CA supports a Cat. 2 classification for the developmental toxicity of pymetrozine.				
Dossier Submitter's Response				
Thank you for the support.				
RAC's response				
Thank you very much. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
04.09.2017	France		MemberState	9
Comment received				
Page 20: Classification proposal Repr. 2; H361f is supported. Page 24: As regard major manifestations of developmental toxicity: - death of the developing organism: early resorptions and postimplantation losses were observed from the mid dose group in rabbit and higher neonatal mortality was observed from the mid dose group in the DNT study in rats. - structural abnormalities: several foetal malformations were observed from mid dose in both species (rat and rabbit), pelvis being a common target. Brain morphometric changes were observed from the low dose in the DNT study. As regard concurrent maternal toxicity: no maternal toxicity was observed in the low and mid dose groups in the DNT study. Maternal toxicity was observed from mid dose in the rat and rabbit developmental toxicity studies. However, neither the severity of maternal toxicity nor any specific mode of action can support that the observed structural abnormalities could be considered as secondary non-specific consequence of other toxic effects. Based on the above considerations, classification Repr. 1B H360D may be triggered as proposed by the Co-RMS of the pesticides procedure (Belgium).				
Dossier Submitter's Response				
Thank you for the support regarding the fertility toxicity classification and the comments regarding the developmental toxicity classification. We agree that the available data set is not completely straightforward. When balancing the arguments increasing and decreasing the level of concern, we concluded that category 2 would be more appropriate.				
RAC's response				
Thank you very much. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2017	United Kingdom	Syngenta	Company-Manufacturer	10
Comment received				
Syngenta consider that pymetrozine does not meet the criteria for classification for an adverse effect on sexual function or fertility. The overall weight-of-the evidence, (detailed in a separate Appendix), is that there is no indication for any direct effect of pymetrozine on spermatogenesis, spermatozoa or the testes, in any species tested, with any potential findings being either secondary to general systemic toxicity (in rats) or a commonly occurring background histopathological finding (in dogs). Combined with the lack of any effect on fertility or reproduction in the 2-generation study, there is no evidence that pymetrozine has a direct effect on the reproductive system. Based on an overall weight of evidence of the reproductive and developmental toxicity data, there is no indication that pymetrozine is associated with a direct effect on foetal development. In the developmental toxicity studies, significant maternal toxicity was observed at the high doses tested in both rats and rabbits. At these dose levels, minor effects on the foetuses, most of which were indicative of only a delay in development, were also observed. There were no treatment-related effects noted on foetal development in the absence of maternal toxicity. In the developmental neurotoxicity study, there was no clear pattern of adverse effects on neurological development. Thus, any changes were considered secondary to the observed maternal toxicity, and as such, no classification is warranted. This position is detailed in a separate Appendix.				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Pymetrozine CLH proposal - Public Comments Fertility and Development Aug 2017.zip
Dossier Submitter's Response
We agree that the available data set is not completely straightforward. When balancing the arguments increasing and decreasing the level of concern, we concluded that category 2 would be more appropriate. None of the further comments supported the position that no classification for reproductive effects would be appropriate. Syngenta has been re-iterating the same arguments since many years, however without ever showing actual data to support its claims. Detailed assessments are included in the annex to the CLH dossier (i.e., Final addendum to the renewal assessment report, sections 2.6.6 and B.6.6). Syngenta's argumentations are centred around "most likely", "suggest" or "consider", i.e., assumptions. Additionally, signs of systemic toxicity are extremely exaggerated by Syngenta. In summary, skeletal changes were induced in developmental toxicity studies in rats and rabbits (displaced pubic bones or reduced pubis, respectively). In the developmental neurotoxicity study in rats, changes in brain morphometry were seen already in the low dose offspring. Additionally, higher neonatal mortality was observed in the mid dose group. Taking into account all findings in developing organisms and those indicating effects on fertility, a classification for reproductive toxicity is considered necessary.
RAC's response
Thank you very much. Noted.

Date	Country	Organisation	Type of Organisation	Comment number
29.08.2017	Netherlands		MemberState	11
Comment received				
Effects on the testis and spermatogenesis were observed in some repeated dose studies in rats and dogs, but not in a two-generation study. It is difficult to determine the severity of the effects, due to the limited reporting of the magnitude and frequency of these effects. However, considering these effects only occurred at high doses and were not found consistently, we tend to agree with the proposal for Cat 2 fertility. Could you provide an overview table per species containing: study duration, exposure route (gavage or diet), exposure level, number of animals and incidence of the effects on the reproductive organs, to allow a better discussion on the proposed classification? For example the highest dose tested in the 2-generation study of 2000 ppm (130 – 150 mg/kg bw/day) inducing no effects on reproductive organs and fertility, was below the dose level at which effects on the reproductive organs in the 28-day studies were reported. Further, with regard to the dog studies, is there anything known whether these dogs reached puberty during the study and whether this could be delayed due to general toxicity? Malformations in the pelvis were observed in both rats and rabbits. The incidence of displaced pubic bones in rats at the high dose was 4/157 (3%), while 3/72 rabbit pups had reduced pubis. Fetal skeletal anomalies and variations consistent with delayed ossification occurred at the mid and high doses in both rats and rabbits; however, these may be related to maternal toxicity. In the rabbit study, early resorptions and post-				

implantation losses were dose-dependently increased in the 75 and 125 mg/kg groups. In particular post-implantation loss was notable, with incidences of 13.1% and 26.3% compared to 3.7% in the controls.
Increased pup mortality was also reported in a developmental neurotoxicity in rats at 38.7 mg/kg/d, as well as alterations of brain morphology. Could you please provide the incidence of these effects in the DNT study in your RCOM?
In the conclusion it is not entirely clear which limited incidences are the main reason to propose Cat 2 for development. Based on only the malformations, we would agree Cat2 is justified. However, we consider that the increase in pup mortality with very limited maternal toxicity in the developmental neurotoxicity study warrants a discussion on classification in Cat 1B.

Dossier Submitter's Response

Thank you for the support. We agree that the available data set is not completely straightforward. When balancing the arguments increasing and decreasing the level of concern, we concluded that category 2 would be more appropriate.

Regarding the comment to provide an overview table, it is referred to Table 17 in the CLH report and to Tables 2.6-7, -8 and -13 in the annex to the CLH dossier (i.e., Final addendum to the renewal assessment report).

Regarding to puberty of the treated dogs, no definitive information is included in the study reports. However, the age of the dogs at study initiation was reported:

- 28-d dog (1991 TOX9652143): 31-33 weeks
- 28-d dog (Author 4, 1998 TOX9851466): 14-17 months
- 90-d dog (1992 TOX9652145; 1992 ASB2012-4620; 1995 TOX9650867): 34-35 weeks
- 1-yr dog (1994 TOX9652153): 24-32 weeks

Regarding to DNT study:
In the present study, dose levels of 0, 100, 500 and 2500 ppm (approx. 8.1, 38.7 and 173.1 mg/kg bw/d) were administered via diet from day 7 of gestation to day 22 postpartum. Due to excessive toxicity the high dose group was terminated and no developmental neurotoxicity examination was performed.

During gestation maternal body weight gain was ca 10 % lower at mid dose level of 500 ppm compared to controls, but without statistical significance and consequently considered of no toxicological concern. Food consumption was decreased during day 1-5 postpartum, however without any influence on maternal body weight. Furthermore, taking into account the high rate of cannibalism at 500 ppm during day 1-5 postpartum, the decreased maternal food consumption seems to be not unexpected. Therefore, the NOAEL for maternal toxicity is considered to be 500 ppm (38.7 mg/kg bw/d) based on excessive toxicity at 2500 ppm.

At 500 ppm an increase in complete litter losses was noted [2/30 (6.7%), 3/30 (10%), 5/29 (17.2%) for control, 100 ppm and 500 ppm, respectively]. Moreover, pup mortality (dead or missing presumed dead) was dose-dependently increased during day 1-5 postnatal. Overall, pup mortality seems comparatively high even at control level, but was neither discussed in the study report nor by Syngenta. According to the study report the intergroup comparison was increased motor activity on isolated time points, only and therefore considered of no toxicological concern.
There were no treatment effects on offspring body weight (gain), food consumption, developmental landmarks, clinical signs, FOB, motor activity, acoustic startle responses, learning and memory or brain weights.

Intergroup comparison of reproductive performance and litter data to day 5 *postpartum*

	Dietary concentration (ppm)			
Observation	**0 (Control)**	**100**	**500**	**2500**
Number mated	30	30	30	30
Number of litters	30	30	29	23
Failed to litter	0	0	1	7
% total litter loss	6.7	10.0	17.2	26.7
Number pups born live	335	339	321	246
% pups born live	95.7	98.2	97.8	97.3
Proportion of litters with all pups born live	23/30	25/30	25/29	18/23
Mean gestation length	22.1	22.0	22.0	22.2
Proportion of male pups – day 1	169/335	162/339	170/321	125/246
% of male pups – day 1	48.5	46.4	53.8	52.3
Proportion of male pups – day 5	145/287	133/282	115/226	44/95
% of male pups – day 5	49.1	46.1	52.0	46.8
Mean litter size Day 1(excl. whole litter losses)	11.5	11.0	10.8	10.7
Mean litter size Day 5 (pre-cull excl. whole litter losses)	10.6	10.4	9.4*	10.6
Mean total litter weight (g) – day 1	63.9	63.8	64.2	62.6
Mean total litter weight (g) – day 5	96.9	91.4	86.3*	93.3
Mean male pup weights (g) – day 1	6.0	5.9	6.1	5.9
Mean male pup weights (g) – day 5	9.4	9.2	9.7	9.3
Mean female pup weights (g) – day 1	5.6	5.6	5.8	5.7
Mean female pup weights (g) – day 5	9.1	8.7	9.2	9.0
Pups found dead	12	8	12	18
Pups missing, presumed dead	37	56	90	59
Pups total dead	49	64	102	77
% dead pups days 1-5	14.6	18.9	31.8	31.3

No statistical analysis performed at 2500 ppm

* Statistically significant difference from control group mean, p<0.05

At the lowest dose level of 100 ppm (8.1 mg/kg bw/d) significant brain morphometry changes were observed (increased thickness of corpus callosum in males on day 63 postnatal, and dorsal cortex in females day 12 postnatal). Brain morphometric changes were also observed at 500 ppm as increased thickness of corpus callosum also on day 12 postnatal in males and of inner granular and molecular layer of the pre-pyramidal fissure in the cerebellum day 63 postnatal in males[1]:

	Males			Females		
Dose level (ppm):	0	100	500	0	100	500
D12 dorsal cortex thickness (level 5)	1.02	1.06	1.07	1.00	1.10**	1.09*
D12 corpus callosum thickness (level 4)	0.60	0.64	0.69*	0.62	0.65	0.64
D63 corpus callosum thickness (level 4)	0.32	0.35*	0.36*	0.31	0.33	0.33
D63 Cerebellum pre-pyramidal fissure thickness of inner granular layer	144	162	172*	156	160	162
D63 Cerebellum pre-pyramidal fissure thickness of molecular layer	206.5	209.9	219.8*	198.0	204.4	210.3

[1] The equipment was calibrated with a graticule or a stage micrometre. However, no units (such as µm) are given in the report, hence the numbers need to be considered as arbitrary units.

RAC's response
Thank you very much. Noted.

Date	Country	Organisation	Type of Organisation	Comment number
01.09.2017	Denmark		MemberState	12
Comment received				
Danish EPA supports the proposed classification repr cat 2. H351fd for the following reasons, but not limited to the following: - effect on spermatogenesis in both dogs and rats - malformations on the pelvis in both rats and rabbits				
Dossier Submitter's Response				
Thank you for the support.				
RAC's response				
Thank you very much. Noted.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2017	United Kingdom		MemberState	13
Comment received				
Hydrolysis and aquatic photolysis endpoints. • It would be useful to clarify the temperatures for quoted DT50 values. Toxicity to Lemna gibba • The CLH report quotes 14 day endpoints. Are 7 days endpoints available as these are preferred for classification? • Please can you clarify if the endpoints are based on growth rate (and if not provide) as the CLH indicates the NOEC is based on non-chlorotic fronds. • As test item concentrations in test media declined over the study, endpoints based on mean measured are preferred. Chronic toxicity to Daphnia magna • We wonder if it would be useful to present 21-day NOEC based on mean measured concentrations for the Grade, 1993 study.				
Dossier Submitter's Response				
<u>Hydrolysis:</u> The temperature for the quoted endpoints at pH 1 (DT_{50}: 3h), pH 5 (DT_{50}:5 - 12d) and pH7 (DT_{50}: approximately 2 years) was 25°C <u>Aquatic photolysis:</u> In the study by Dixon & Gilbert (2011c) the temperature was 25°C (DT_{50}: <1 d under continuous irradiation with 25.4 W/m^2, corresponding to 1 day of UK/US summer sunlight) The estimated DT_{50} (6.8 and 4.3d) in previous studies (per-reviewed in the DAR, 2004) for pyridinyl- and triazinyl-labelled pymetrozine are relate to 12-h day of latitude 40°N. The temperature during these studies (Kirkpatrick 1995c & d) were 25°C. In the study by Mamouni (2004) the temperature was 24.9±0.9°C (DT_{50}: 15.1 d, 12 h light/12 h dark with 44 W/m^2 in sterile natural pond water, corresponding to 22.6 ± 0.8 days natural summer sunlight at latitudes of 30 to 50°N)				

Toxicity to Lemna gibba:
Although 7 day endpoints are preferred for classification, results at 7 days for growth of Lemna were not stated in the study report, unfortunately.
The NOEC is based on growth (frond number increase) at 14 days. It is an additional information from the study, that the fronds are non-chlorotic.
The use of mean measured concentrations is preferred, if the concentration declined more than 20% over the study. In the study the concentration of test substance only at the start and at the end (day 14) were measured. The measured concentrations at 14 days were for all tested concentrations less than the analytical detection limit (5.06 mg/L).
According the "Outcome of the pesticides peer review meeting on general recurring issues in ecotoxicology" of EFSA, 2015 it is recommended, that such study results, where a suitable exposure throughout the whole test period was not demonstrated, none of the endpoints must be used in first tier risk assessment. Moreover when the test concentrations were not maintained and significant residues were not present at the end of the exposure period, the validity of the study should be questioned.
Therefore, the study results are only supportive and not relevant for classification.

Chronic toxicity to Daphnia magna:
The key study (Boeri, 1995) for chronic toxicity to Daphnia magna revealed a NOEC (21 days) of 0.025 mg/L (mean measured) in a flow-through system.
At the supportive study (Grade, 1993) for chronic toxicity to Daphnia magna a NOEC (21 days) of 0.0785 mg/L (mean measured) in a semi-static system was determined.

RAC's response

RAC agrees in considering the *Lemna* study as only supportive information. The EFSA conclusion states that "*When the test concentrations were not maintained and significant residues were not present at the end of the exposure period (or at the end of the renewal period for semi-static design), the validity of the study should be questioned*" and adds "*When only initial and final measurements are available and no concentrations were detected at study end, the use of the LOD or half of LOQ is not supported. This is because it is not known when the concentrations decreased to practically zero (<LOD). The usefulness of such studies in first tier risk assessments should be questioned*."

RAC agrees in considering the study by Boeri (1995) the key study for chronic toxicity to *Daphnia*. The Grade (1993) study has deviations such as pH variation and time passed till the first brood. Both points are not in fulfilment with the OECD validity criteria 202 Part II. In addition, the number of living offspring produced per parent animal surviving at the end of the test (52) is lower than current requirements for validity of the test ≥60. Mean measured concentrations are more appropriate since the test substance concentrations vary by more than 20% of the nominal concentration.

Date	Country	Organisation	Type of Organisation	Comment number
04.09.2017	France		MemberState	14
Comment received				
FR agrees with the proposed classification and chronic M factor.				
Dossier Submitter's Response				
Thank you, for your comment.				
RAC's response				
Noted				

PUBLIC ATTACHMENTS
1. Pymetrozine CLH proposal - Public Comments Fertility and Development Aug 2017.zip
[Please refer to comment No. 10]