Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

pyridate (ISO); O-(6-chloro-3-phenylpyridazin-4-yl) S-octyl thiocarbonate

EC Number: 259-686-7
CAS Number: 55512-33-9

CLH-O-0000001412-86-186/F

Adopted

5 December 2017

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON PYRIDATE (ISO); O-(6-CHLORO-3-PHENYLPYRIDAZIN- 4-YL) S-OCTYL THIOCARBONATE

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: pyridate (ISO); O-(6-chloro-3-phenylpyridazin- 4-yl) S-octyl thiocarbonate
EC number: 259-686-7
CAS number: 55512-33-9
Dossier submitter: Austria

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
21.02.2017	France		MemberState	1
Comment received				
We agree with the classification proposal				
Dossier Submitter's Response				
Noted, please consider DS response to comment 2				
RAC's response				
Noted				

Date	Country	Organisation	Type of Organisation	Comment number
24.02.2017	Belgium	Belchim Crop Protection	Company-Manufacturer	2
Comment received				
section 3.3 STOT SE & 3.8 STOT RE. Belchim Crop Protection does not agree with the proposed conclusion based on different interpretation on study results and new data				
Dossier Submitter's Response				
As detailed in comments 2, 9, and 15, the Manufacturer Belchim Crop Protection disagrees with classification as STOT SE and STOT RE. The clinical observations in the dog studies are considered signs of general toxicity rather than specific neurotoxic effects. New data (an Acute Single Dose Oral Gavage Neurotoxicity Study in Rats compliant to guideline EPA OPPTS 870.6200) and a position paper summarizing this study and the company position have been submitted. This study and the position paper have not been available for re-newal and have thus neither been summarized in the RAR nor peer reviewed:				

1) Diehl, L (2016). Pyridate. Acute Single-Dose Oral Gavage Neurotoxicity Screening Study in Rats. Report 200971881.

2) Pyridate. Discussion of potential STOT classification regarding neurotoxicity Toxconsult LLC (2017).

Therefore, a brief assessment of the provided study and argumentation is presented here (an up-date or revision of the CLH report to incorporate this new information is not foreseen).

Acute Single-Dose Oral Gavage Neurotoxicity Screening Study in Rats

Test Guidelines: EPA-OPPTS 870.6200
Diehl LM, 2016
Report No 20097188
Test substance: Pyridate
Batch (lot) number: 051, expiry date Nov 1st, 2017
Purity: 91.01%
Vehicle: corn oil
Rat strain: Crl:CD(SD) Sprague Dawley, approx. 8 weeks old at dosing

The study is considered fully guideline-compliant, no deviations affecting the integrity of the study or the interpretation of the study results are mentioned in the report.

Phase A:
5 male and 5 female rats were dosed with 0, 500, or 1000 mg/kg bw pyridate to establish dose levels for phase B and to determine the time- of –peak- effect (TOPE) for neurological effects.

The following parameters and end-points were evaluated:
-clinical signs
-body weights and body weight gains
-food consumption
-gross necropsy findings

Mortality (for details refer to study report Table 1 and Appendix 4)
In the top dose group (1000mg/kg bw), 3 females were fond dead, and 2 males and 2 females were euthanized in moribund condition following dosing.
In the 500 mg/kg bw dose group, 1 female animal was found dead.

Parameter	Dose (mg/kg bw)		
	0	500	1000
Males n=	5	5	5
Found dead (day)	-	-	-
Unscheduled euthanasia (day)	-	-	2 (1)
Females n=	5	5	5
Found dead (day)	-	1 (1)	3 (1)
Unscheduled euthanasia (day)	-	-	2 (1)

Days of occurrence in brackets (day 1 = start)

Table from submitted position paper: Pyridate. Discussion of potential STOT classification regarding neurotoxicity.Toxconsult LLC (2017).

Phase B:
10 male and 10 female rats were dosed with 0, 60, 177 or 500 mg/kg bw pyridate.

The following parameters and end-points were evaluated:
-clinical signs
-body weights and body weight gains
-food consumption
-full functional observational battery (FOB)
-motor activity
-gross necropsy findings
-organ weights
-histopathologic examinations

Mortality
In the top dose group (500mg/kg bw), 1 male animal was found dead and 1 female was euthanized in moribund condition.

Parameter	Dose (mg/kg bw)			
	0	62.5	177	500
Males n=	10	10	10	10
Found dead (day)	-	-	-	1 (1)
Unscheduled euthanasia (day)	-	-	-	-
Females n=	10	10	10	10
Found dead (day)	-	-	-	-
Unscheduled euthanasia (day)	-	-	-	1 (1)

Days of occurrence in brackets (day 1 = start)

Table from submitted position paper: Pyridate. Discussion of potential STOT classification regarding neurotoxicity.Toxconsult LLC (2017).

Clinical signs were observed at dose levels where mortality was observed:

Parameter	Doses (mg/kg bw)				
	0	62.5	177	500	1000
Preliminary study					
Mortality	-	./.	./.	+	+
Clinical signs	-	./.	./.	+	+
Main study					
Mortality	-	-	-	+	./.
Clinical signs	-	-	-	+	./.
FOB effects	-	-	-	+	./.

./. = dose not used in the study

Table from submitted position paper: Pyridate. Discussion of potential STOT classification regarding neurotoxicity.Toxconsult LLC (2017).

At 500and 1000 mg/kg bw, decreased activity, incoordination, weakness, abnormal breathing (i.e., abnormal sounds, irregular rate, increased respiratory rate, labored or shallow breathing), lying on side, non-sustained convulsions, tremors, and locomotor stereotypy were noted prior to death. Based on these results it can be assumed that doses of 500 and 1000 mg/kg bw were clearly lethal doses, beyond MTD (there were also clear,transient effects of body weight gain and food consumption), which caused similar signs in the surviving animals like in animals which died and thus are regarded as signs of acute unspecific toxicity. They began approximately 1 hour post-dose with recovery in

almost all cases on the following day. In summary, these signs are regarded as unspecific and reversible clinical signs of animals under stress after exposure to lethal doses and not of a specific neurotoxic potential.

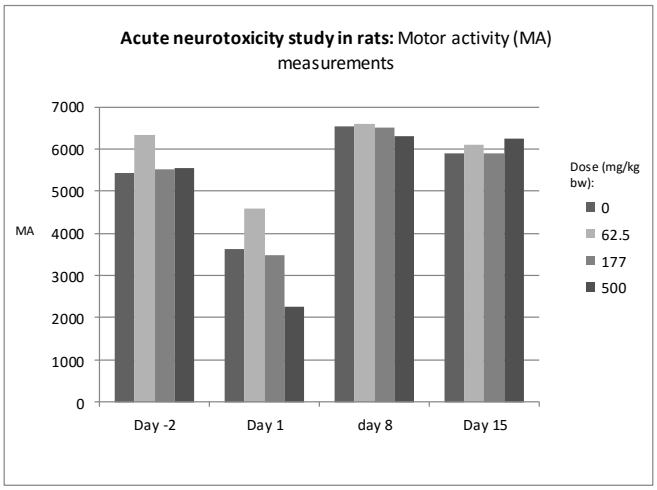

Table from submitted position paper: Pyridate. Discussion of potential STOT classification regarding neurotoxicity.Toxconsult LLC (2017)

Based on mortality at doses >500 mg/kg bw, classification as Acute Tox (Oral) Cat 4, H302 is considered justified by the DS.

RAC's response
Thank you for the clear summary of the new study. RAC agrees with the interpretation provided by the DS.

Date	Country	Organisation	Type of Organisation	Comment number
20.02.2017	Germany		MemberState	3
Comment received				
Besides to some comments on specific hazards, we generally agree with the classification proposals. However, we noticed that the hazard pictograms GHS07, GHS08 and GHS09 are missing (page 8).				
Dossier Submitter's Response				
Noted, it is not possible to revise the CLH-report at this stage				
RAC's response				
Noted				

Date	Country	Organisation	Type of Organisation	Comment number
24.02.2017	Norway		MemberState	4
Comment received				
NO agrees to the proposed classification from Austria on Pyridate: Skin Irrit. 2, H315 Skin Sens. 1B, H317 STOT SE 1, H370 Aquatic Acute 1, H400 Aquatic Acute 1, H400, M-factor = 1 Aquatic Chronic 1, H410				

Aquatic Chronic 1, H410, M-factor = 10
Dossier Submitter's Response
Noted, please consider DS response to comment 2, 10, 15, 16 and 17
RAC's response
Noted

Date	Country	Organisation	Type of Organisation	Comment number
24.02.2017	Sweden		MemberState	5
Comment received				
We note that the hazard class skin sensitization is not open for commenting. However, the DS has proposed a change from the previous harmonised classification of Skin Sens. 1 to subcategorisation in 1B. Our comments are as follows: Two animal studies are available for assessing the skin sensitization potential of pyridate; one Magnusson and Klingman test not including controls indicating strong potency (100% of animals with positive reactions at 1% intradermal induction dose) and one Buehler test suggesting a lower potency (16% of animals with positive reactions at 10% induction dose). The Swedish CA does not consider the human data which is included in the CLH-report relevant for the purpose of assessing skin sensitisation potential under CLP, as this is only summary reports from a secondary source. For Category 1, when a non-adjuvant Guinea pig test method is used, a response in at least 15% of the animals is considered positive. For an adjuvant test the corresponding number is 30%. Based on the results from the two animal studies, pyridate fulfills this criteria. The lack of detail in the CLH- report makes it however difficult to conclude on subcategorization. It is unfortunate that the Magnusson and Klingman study lacked control animals. It may be that the vehicle used for the challenge resulted in irritancy reactions in the animals which were mistaken for sensitization. This is however difficult to conclude on without knowing which vehicle was used in the test. Also, the Buehler test is in general considered less sensitive than an adjuvant type test such as the Magnusson and Klingman, something which may in part explain the lower frequency of positive responses obtained in that study. The purity of the test material will also influence the results, and is important information in order to properly assess the skin sensitization potential of pyridate. There is a general lack of detail in the reporting of the animal studies in the CLH-report. For both studies, please include the purity of test substance and the vehicle. Also please specify deviations from OECD guideline 406 and compliance with GLP for each study. Was there a dose selection study performed prior to the Magnusson and Klingman test? If so, please include the results in the CLH-report. If the information is lacking from the original studies – please state it in the CLH-report. We also lack a substantial discussion of the results and the reliability of the studies, as well as a conclusion based on the above to arrive at the proposed classification (Skin Sens. 1B).				
Dossier Submitter's Response				
Studies on the potential for sensitisation were performed 1976 and 1988 (GLP was formally adopted in the EU in 1987). Studies were summarized to the level of detail that is available from the study reports. No up-date of the CLH report is foreseen for procedural reasons at this stage. As detailed in section 3.6.1.4 of the CLH report, the available animal tests give ambiguous results regarding Category 1A and 1B. Category 1B was the peer review proposal. Please also refer to commenting box 7.				

RAC's response
Noted. The comments from Sweden are relevant and are taken into account in the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
22.02.2017	Denmark		MemberState	6
Comment received				
The comments below are all included in the uploaded attachment. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments to the CLH report on pyridate.docx				
Dossier Submitter's Response				
Comment is provided inthis table, see comment number 17. Response is also provided in commenting box 17				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
24.02.2017	Spain		MemberState	7
Comment received				
3.6.1.3 Summary and discussion of skin sensitisation Pyridate was sensitising to the skin in the Magnusson and Kligman Test for 100% of the animals responding to 1% intradermal induction dose, which is consistent with sub-category 1A (≥ 60 % responding at > 0,1 % to ≤ 1 % intradermal induction dose). No control group was included in this study. Pyridate was sensitising to the skin in the Buehler Test for 33.3% of the animals responding to 3% topical induction dose, which is consistent with sub-category 1B (≥ 15 % to < 60 % responding at > 0,2 % to ≤ 20 % induction concentration). According to the Guidance on the Application of the CLP Criteria (ECHA, Jun 2015), "Classification into sub-categories is only allowed if data are sufficient (CLP Annex I 3.4.2.2.1.1). Care should be taken when classifying substances into Category 1B when Category 1A cannot be excluded. Unless there is sufficient evidence to place such substances in sub category 1A or 1B, classification in category 1 should be the default position. In other words, although the criteria in the table 3.4.4 for classification to subcategory 1B are fulfilled, the classification for subcategory 1A may not be excluded and therefore the substance should be classified as a Category 1 skin sensitiser" The proposal of the dossier submitter is classification as Skin sensitiser 1B, H317. In opinion of the Spanish CA, Category 1A cannot be excluded taking into account the results of the maximization study. Therefore, in our opinion, the current classification as Skin sensitiser 1, H317, inserted in Annex VI of Regulation CLP should be maintained.				
Dossier Submitter's Response				
Please refer also to comment number 5. The argumentation presented above is considered valid by the DS. According to Guidance on the Application of the CLP Criteria (ECHA, Jun 2015), unless there is sufficient evidence to place substances in sub category 1A or 1B, classification in Category 1 should be the default position.				

RAC's response
Noted; RAC agrees.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
21.02.2017	France		MemberState	8
Comment received				
We agree with the classification proposal regarding Specific target organ toxicity – single exposure				
Dossier Submitter's Response				
Noted, please consider DS response to comment 2, 10, 15, 16 and 17				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
24.02.2017	Belgium	Belchim Crop Protection	Company-Manufacturer	9
Comment received				
It is concluded that clinical signs in the toxicity studies with pyridate occurred at peri-lethal doses and consisted of general and unspecific signs of toxicity but not of direct specific neurotoxicity. With regard to a possible STOT-SE classification, this should only be considered if there is clear evidence of toxicity to a specific organ especially when it is observed in the absence of lethality. However, in the toxicity studies in rats and dogs, clinical signs of acute toxicity occurred at peri-lethal doses. A few myelin findings in some dog studies were seen which were not dose- and thus not treatment-related. They are background in aging animals and are not associated with a delayed neurotoxic potential which is caused by an axonopathy which did not occur after pyridate. A lack of acute neurotoxic potential was demonstrated in a guideline study with pyridate according to EPA-OPPTS (870.6200) test guidelines. In this study no evidence of acute neurotoxicity of pyridate was observed and no histopathological changes in the nervous system were seen. Based on this study an acute neurotoxic potential of pyridate can be excluded. Since the unspecific toxicity signs were acute effects, similar to that in the acute toxicity studies, with rapid reversibility, often on the same day, also a neurotoxic potential after repeated dosing can be ruled out. Furthermore, despite a long time of agricultural usage no reports about human poisoning cases with neurotoxic consequences are known. Therefore, based on all arguments no evidence of a direct specific acute or subchronic neurotoxic potential of pyridate exists, so that a STOT-SE or STOT-RE classification is not warranted. Above argumentation is documented in: 1. Pyridate Toxconsult LLC (2017). Discussion of potential STOT classification regarding neurotoxicity 2. Diehl, L (2016). Pyridate. Acute Single-Dose Oral Gavage Neurotoxicity Screening Study in Rats. Report 20097188				
Dossier Submitter's Response				
Noted, please consider DS response to comment 2, 10, 15, 16 and 17				

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
20.02.2017	Germany		MemberState	10

Comment received

Considering the results in the developmental toxicity study in rats, pregnant rats seem to be more susceptible to single doses of pyridate than non-pregnant animals. 13 of 25 pregnant rats died after a single dose of 495 mg/kg bw pyridate (p. 79 of the CLH dossier). These results might be sufficient to classify pyridate with Acute tox. 4 (H302) for the oral route.

Considering the presented results, the M&K test points towards Cat. 1A and the Buehler test towards Cat. 1B (but cannot exclude cat. 1A). In line with Example 8 of the CLP-GD (chapter 3.4.6.1.8), this data set would lead to Cat. 1A.

Dossier Submitter's Response

Please also consider DS response to comment 2, 15, 16, and 17 for classification for acute oral toxicity.
For skin sensitisation, responses are provided in commenting boxes 5 and 7.

All previously available studies acute oral toxicity performed with different strains and vehicles did not lead to classification of pyridate, as LD50 values were consistently above the trigger value of 2000 mg/kg bw.
Now, a new a new study (Diehl, L (2016). Pyridate. Acute Single-Dose Oral Gavage Neurotoxicity Screening Study in Rats. Report 20097188) is available, supporting classification of pyridate as Acute Tox (Oral) Cat 4, H302 (see study evaluation in commenting box 2).

The previously available studies did not support classification (study report dates from 1984-1988). The studies were generally judged to be of sufficient quality and reliability to support classification decisions. It is now a guideline requirement that veterinarians/ animal technicians euthanize any animal that is found near death or suffering from intractable pain. In the above cited newly performed study, several animals were euthanized for humane reasons. This is, in addition to general variability between laboratories and animal strains, considered to contribute to the diverging study results.

The mortality observed in the rat developmental toxicity study and its relevance for classification was discussed in the CLH-report (Section 3.2.4):
All estimated LD_{50} and LC_{50} values are above the criteria for triggering classification and labelling. However, in the OECD testing guidelines for acute toxicity it is stated that "females should be nulliparous and non-pregnant". Therefore, mortality after a single gavage dose to pregnant animals was not considered for classification for acute toxicity. The dossier submitter (Austria) would like to highlight that in the rat developmental toxicity study overt maternal toxicity resulting in 13/25 deaths > 465 mg/kg bw after application of a single dose (via gavage, vehicle distilled water with 4% carboxy methylcellulose sodium salt) was observed (see section 3.11.2.1). No other factors possibly influencing survival in the two highest dose groups are described in the study report. No specific guidance in the CLP regulation and associated guidance on the relevance of this effect is known to the dossier submitter except for a short note in the "Guidance on the application of CLP criteria, Version 4.1, June 2015, section 3.7.2.3.1, stating that for repeat dose tests, extrapolation form non-pregnant to pregnant animals cannot easily be performed.

DS considers that the mortality observed in the developmental study 13/25 deaths > 465 mg/kg bw is in line with the observations from the Diel et al study, and also supports classification for acute oral toxicity.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
24.02.2017	Norway		MemberState	11
Comment received				
p 34-36: Acute oral toxicity: NO are of the opinion that the toxicity of pyridate to the pregnant rats in the teratology studies should be taken into consideration and be discussed concerning classifying for acute oral toxicity. Classification for acute toxicity should cover all subgroups of a population. For an oral LD50 around 465 mg/kg bw this would result in a classification into Acute toxicity, Category 4, and come in addition to the STOT SE 1 classification.				
Dossier Submitter's Response				
Please refer to comment number 10				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
24.02.2017	Sweden		MemberState	12
Comment received				
n.a				
Dossier Submitter's Response				
-				
RAC's response				
-				

Date	Country	Organisation	Type of Organisation	Comment number
22.02.2017	Denmark		MemberState	13
Comment received				
STOT SE 1: The proposal to classify with STOT SE 1 is supported based on the data in the CLH-report. It was noted, however, that in one of the position papers from the applicant (Kobel W, 2012) included as an annex to the CLH report, it is stated (p. 151) that 'potentially relevant observations were (…) not seen in the initial phases of the repeat dose gavage studies in rats and dogs'. The onset of clinical signs in dogs after a single dose should be confirmed in the study reports. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments to the CLH report on pyridate.docx				
Dossier Submitter's Response				
Please refer to response in commenting box 17				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
24.02.2017	Spain		MemberState	14
Comment received				
Clinical signs related to neurotoxicity were consistently observed in oral gavage studies in rats (acute studies) and in repeated dose studies in rats and dogs with onset of signs 1-3 hours after dosing. After single exposure in 90-day dog studies, the signs (ataxia, sedation, dyspnea, uncoordinated movements, tremor) were observed below 300 mg/kg bw per day, within the guidance value range for STOT SE Category 1. The Spanish CA support the proposed classification as STOT SE Category 1.				
Dossier Submitter's Response				
Noted, please consider DS response to comment 2, 10, 15, 16 and 17				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
24.02.2017	Belgium	Belchim Crop Protection	Company-Manufacturer	15
Comment received				
It is concluded that clinical signs in the toxicity studies with pyridate occurred at peri-lethal doses and consisted of general and unspecific signs of toxicity but not of direct specific neurotoxicity. With regard to a possible STOT-SE classification, this should only be considered if there is clear evidence of toxicity to a specific organ especially when it is observed in the absence of lethality. However, in the toxicity studies in rats and dogs, clinical signs of acute toxicity occurred at peri-lethal doses. A few myelin findings in some dog studies were seen which were not dose- and thus not treatment-related. They are background in aging animals and are not associated with a delayed neurotoxic potential which is caused by an axonopathy which did not occur after pyridate. A lack of acute neurotoxic potential was demonstrated in a guideline study with pyridate according to EPA-OPPTS (870.6200) test guidelines. In this study no evidence of acute neurotoxicity of pyridate was observed and no histopathological changes in the nervous system were seen. Based on this study an acute neurotoxic potential of pyridate can be excluded. Since the unspecific toxicity signs were acute effects, similar to that in the acute toxicity studies, with rapid reversibility, often on the same day, also a neurotoxic potential after repeated dosing can be ruled out. Furthermore, despite a long time of agricultural usage no reports about human poisoning cases with neurotoxic consequences are known. Therefore, based on all arguments no evidence of a direct specific acute or subchronic neurotoxic potential of pyridate exists, so that a STOT-SE or STOT-RE classification is not warranted. Above argumentation is documented in: 1. Pyridate Toxconsult LLC (2017). Discussion of potential STOT classification regarding neurotoxicity 2. Diehl, L (2016). Pyridate. Acute Single-Dose Oral Gavage Neurotoxicity Screening Study in Rats. Report 20097188				

Dossier Submitter's Response
The manufacturer has provided detailed argumentation regarding the toxicity profile of pyridate observed in various studies. DS considers the information presented highly relevant. A brief summary of the main argumentation is presented here, for a detailed description please refer to the submitted information: In Pyridate. Toxconsult LLC (2017). Discussion of potential STOT classification regarding neurotoxicity, argumentation is presented why the effects caused by pyridate administration are considered signs of unspecific, systemic toxicity rather than specific neurotoxicity: -) Clinical signs in acute toxicity studies in rats (lethargy, sedation, hunched posture, ventral body position, uncoordinated movements, lateral recumbency, dyspnea and labored breathing) are considered signs of impending death (see OECD ENV/JM/MONO(2000)7) and thus are regarded as sings of systemic acute toxicity -) Reversibility of clinical signs: the clinical signs of pyridate in rats were reversible within hours, and or within the recovery period, indicating no functional damage to the nervous tissue. -) Dog studies Clinical signs resembling neurotoxicity are observed at dose levels which were (peri)lethal and where the MTD was exceeded (reductions in body weight gain, food consumption, other signs of general toxicity like emesis and salivation). -) No evidence of any axonal change/ other findins in the nervous system (myelin findings are considered background findings with a high variability and are not considered test substance related) Overall, it was concluded by the manufacturer that the clinical signs which resemble signs of neurotoxicity were unspecific signs of acute toxicity or poisoning which occurred only at doses which were lethal or close to the lethal range, and clearly above the MTD. The dog seemed to be more sensitive and showed a different pattern than rats. In conclusion, the DS considers the argumentation presented scientifically sound and valid. In the light of the new study on acute neurotoxicity, classification for acute oral toxicity (Cat 4, H302) seems more appropriate than classification for STOT SE/RE.
RAC's response
Thank you for the additional points; they help in the consideration of the applicability of STOT SE/RE.

Date	Country	Organisation	Type of Organisation	Comment number
24.02.2017	Norway		MemberState	16
Comment received				
p 60-61: STOT RE 2:The re-evaluation of the demyelination of the sciatic nerve after repeat dose studies in the dog, described this effect as myelin digesting chambers and by the pathology claimed as not severe. However, myelin digesting chambers are now seen as the hallmark of Wallerian degradation that takes place after axonal injury. This effect that might have another cause than the clinical symptoms (basis for STOT SE 1) could warrant the classification with STOT RE 2. The dose level at which this effect occurs seems to be between 80 and 120 mg/kg bw /day.				

Dossier Submitter's Response
The occurrence and severity of the finding "mylin digestion chambers" have been summarized in the CLH-report in chapter 3.7.1.6. While Wallerian degeneration is, to our knowledge, indeed a hallmark of neurodegenerative diseases, it is not observed in isolation. No other histopathological observations were made in any of the long term studies in any species tested. Thus, classification based for STOT RE based on this finding is not supported by the DS.
RAC's response
The lack of consistent findings associated with neurodegenerative disease across all the available studies and within studies is noted.

Date	Country	Organisation	Type of Organisation	Comment number
22.02.2017	Denmark		MemberState	17
Comment received				
STOT RE 2: Additional classification also with STOT RE 2 may be considered based on the following observations in the dog studies: 1) It appears from the clinical signs in dogs in relation to acute effects (table 16 in the CLH report) compared with the long-term effects (table 50 in the CLH report) that the clinical signs of neurotoxicity are more severe at the same dose after repeated dosing in both 90-d dog studies (see data highlighted in yellow below). 2) A mild exacerbation of clinical signs may also be reflected in the experts proposal of a combined NOAEL of 60 mg/kg bw per day for acute effects in the 90-day dog studies and on a combined NOAEL of 40 mg/kg bw per day for repeated dose effects in the 90-day dog studies. 3) In one of the position papers from the applicant (Kobel W, 2010) included as an annex to the CLH report, it is stated (p. 148) that 'In the first subchronic study, emesis, ataxia, opisthotonus, hypoactivity, salivation, mydriasis, nystagmus, head swing, muscle fasciculations, rarely also head tilt were noted at 200, less at 60 mg/kg. Onset was 1 – 3 h after dosing, returning to normal within 24 hours up to 19 days. Recovery thereafter was not always complete. It should be mentioned that the above considerations regarding classification were made under the assumption that the rat-specific guidance values for STOT classification are to be used for dogs without allometric scaling. 90-d dog study, clinical signs (Tomkins, 1987) Table 16 (single exposure) ≥ 60 mg/kg bw: Emesis ≥ 200 mg/kg bw: Ataxia, hypoactivity, opisthotonus, muscle fasciculations, head swing, nystagmus, mydriasis, salivation Table 50 (repeated exposure) ≥ 60 mg/kg bw/d: Clinical signs (emesis, salivation, ataxia, mydriasis, nystagmus)				

90-d dog study, clinical signs (Vandaele, 1990)
Table 16 (single exposure)
≥ 80 mg/kg bw:
Underactivity (F)
≥ 120 mg/kg bw: Ataxia,
emesis, opisthotonus

Table 50 (repeated exposure)
≥ 80 mg/kg bw/d: Clinical signs
(salivation, ataxia, hunched
posture, emesis, pupils dilated,
head shaking, underactivity), ☐
erythrocyte parameters, ☐
Heinz bodies, ☐☐relative liver
and kidney weight,
histopathological changes in the
liver (pigmentation in Kupffer
cells)
≥ 120 mg/kg bw/d: ☐☐bw gain
(F), clinical signs
(opisthotonus, tremor,
prostration), ☐☐HB, changes in
organ weight and haematology,
myelin digestion chambers

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments to the CLH report on pyridate.docx

Dossier Submitter's Response

According to the Guidance on the Application of the CLP Criteria (ECHA, Jun 2015)
"Where the same target organ toxicity of similar severity is observed after single and repeated exposure to a similar dose, it may be concluded that the toxicity is essentially an acute (i.e. single exposure) effect with no accumulation or exacerbation of the toxicity with repeated exposure. In such a case classification with STOT-SE only would be appropriate."

No accumulation or exacerbation of the toxicity is seen after repeated application. Therefore the DS had considered that the effects after repeated application are already covered by STOT-SE.

However, new data on the neurotoxic potential of pyridate has been submitted, indicating that the effects are signs of unspecific, acute toxicity rather than specific neurotoxic effects.

According to the Guidance on the Application of the CLP Criteria (ECHA, Jun 2015)
"*There are two hazard classes for single exposure toxicity: 'Acute toxicity' and 'STOT-SE'. These are independent of each other and both may be assigned to a substance or a mixture if the respective criteria are met. Acute toxicity refers to lethality and STOT-SE to non lethal effects. However, care should be taken not to assign both classes for the same toxic effect, essentially giving a 'double classification', even where the criteria for both classes are fulfilled. In such a case the most appropriate class should be assigned.*
Acute toxicity classification is generally assigned on the basis of evident lethality (e.g. an LD50/LC50 value) or where the potential to cause lethality can be concluded from evident toxicity (e.g. from fixed dose procedure). STOT-SE should be considered where there is clear evidence of toxicity to a specific organ especially when it is observed in the absence of lethality."

Therefore, the DS considers classification for Acute Toxicity (oral) Cat4, H302 justified and more appropriate than STOT-SE/RE, since clear evidence for specific neurotoxic effects in the absence of lethality are lacking.
RAC's response
Noted, as the DS has commented, the guidance seems helpful on this matter.

Date	Country	Organisation	Type of Organisation	Comment number
21.02.2017	France		MemberState	18
Comment received				
We agree with the classification proposal regarding Specific target organ toxicity – repeated exposure				
Dossier Submitter's Response				
Noted, please consider DS response to comment 2, 10, 15, 16 and 17				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
24.02.2017	Spain		MemberState	19
Comment received				
According to the Guidance on the Application of the CLP Criteria (ECHA, Jun 2015) "Where the same target organ toxicity of similar severity is observed after single and repeated exposure to a similar dose, it may be concluded that the toxicity is essentially an acute (i.e. single exposure) effect with no accumulation or exacerbation of the toxicity with repeated exposure. In such a case classification with STOT-SE only would be appropriate." After single and repeated dose clinical signs related to neurotoxicity in dogs in the same dose range are the most severe effect. No accumulation or exacerbation of the toxicity is seen after repeated application and these neurological clinical signs are essentially reversible. Therefore, we agree with the dossier submitter to consider that a classification for STOT-SE solely is more appropriate than classification for both STOT-SE and STOT-RE. Therefore the Spanish CA considers that effects after repeated application are already covered by STOT-SE.				
Dossier Submitter's Response				
Noted, please consider DS response to comment 2, 10, 15, 16 and 17				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
24.02.2017	Belgium	Belchim Crop Protection	Company-Manufacturer	20
Comment received				
no comments				

Dossier Submitter's Response
Noted.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
22.02.2017	Denmark		MemberState	21
Comment received				
We agree with the proposal of the CHL report. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comments to the CLH report on pyridate.docx				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
06.02.2017	United Kingdom		MemberState	22
Comment received				
The CLH report includes a whole fish BCF of 116 for pyridate. There are no study details and it is unclear if: 1) the study method was appropriate given the potential for rapid hydrolysis; 2) the BCF reflects steady-state; or 3) the BCF reflects a relevant species or lipid concentration. However, we note that this does not impact the classification given the substance is considered not rapidly degradable. Based on available data, the most sensitive chronic endpoint is the 21-day NOEC for Daphnia magna. Given the presented information, it is unclear if the proposed value of 0.01 mg a.i./l is appropriate for classification given hydrolysis (especially at test temperature and pH) to the biologically active degradant pyridafol. It is unclear if the observed response is induced by the parent, the degradant or a combination effect. It would be useful to provide analytical data across the renewal periods for the parent and degradant. In addition, it is currently not clear if the mean measured value relates to a time-weighted mean which may be appropriate. We note a chronic toxicity study to Daphnia magna is available for pyridafol with a 21-day NOEC of 5 mg a.i./l based on nominal concentrations. It would be useful to provide further details of this study including validity criteria and analytical information.				
Dossier Submitter's Response				
Response to comment on BCF: The study to determine the BCF was evaluated already in the first DAR for Annex I inclusion of Pyridate according to Directive 91/414. For reasons of completesness, the summary included in the first DAR is given below: In a flow-through test bluegill sunfish were exposed to a nominal concentration of 0.05 mg/L of radiolabelled test substance for 28 days followed by a 14 day depuration period. The level of radioactivity in the treated tanks was 0.05 mg Pyridate equivalent per litre,				

24.8 % of the total radioactivity in the test medium was determined as Pyridate, 55.3 % as CL9673. Pyridate and its main degradation product CL9673 were accumulated to a limited extent. The plateau level was achieved after 3 days of exposure and represented on average 116, 27 and 180, respectively for the fish, edible and non-edible tissues. Depuration was very rapid with a calculated elimisation half-life of 1.2 to 4.5 hours, which was in line with the instability of Pyridate and the polar nature of the degradation products. The log Pow of CL9673 is 0.5 at pH 7 (Ellgehausen, Wüthrich 1984).

The study was conducted under flow-through conditions and a plateau level was achieved. The study was conducted with bluegill sunfish.

Response to comment on the 21-day NOEC for Daphnia magna:
As explained in the comment of the RMS, the endpoints included in the study summary were based on the sum of measured pyridate and measured pyridafol (CL9673) expressed as pyridate. The NOEC for effects on reproduction and parent mortality were however proposed to be set to 0.01 mg ai/L (the limit of detection) based on the low measured concentrations of pyridate alone, what is considered to be a quite conservative approach. Actually it is very difficult or almost impossible to test Pyridate alone as it rapidly degrades to its first metabolite. Effects are therefore always likely to be caused by a mixture of the parent and the metabolite. The proportion of the parent can be increased by flow-through or semistatic-tests, but still both compounds will be present. It is regarded as a worst-case to assign the observed effects to one compound. As the study was conducted to assess effects of pyridat, the endpoint was based on pyridat.

Response to comment on the chronic daphia study on pyridafol:
According to the renewal assessment report for approval according to Regulation 1107/2009,the study by Wüthrich (1991e) was considered to be still of relevance for the risk assessment. The validity criteria according to the cited guidelines were met: The mortality in the controls did not exceed 20% at the end of the test. The dissolved oxygen concentration was >60% (5 mg/L) throughout the test. The deviation of the pH from the initial value was <0.3 units. The first young were born in the controls after nine days. The average cumulative number of young per female in the water control was 85 and in the solvent control 83.
The number of tested animals and replicates deviated from the cited guideline as 10 daphnids (out of 25) were tested individually instead of 4 replicates with ten daphnids each. As this test regime is in line with current recommendations according to OECD 211, this deviation is not considered to invalidate the test. The endpoint is based on nominal values. In addition to mortality and effects on reproduction effects on the body length of all surviving daphnids were investigated. No significant difference was noted.

RAC's response

RAC also sees the questions asked by the Member State and answered by the Dossier Submitter important in drafting the ODD.

Date	Country	Organisation	Type of Organisation	Comment number
20.02.2017	Germany		MemberState	23

Comment received

Page 128 point 4.4.3 Algae and aquatic plants:
The study of Grade, 1998 with Anabaena flos-aquae does not fulfill the validity criteria for toxicity tests to algae (according to OECD 201). The coefficient of variation of sectional specific growth rate does not meet the validity criteria (≤ 35%).
There are no other tests available for aquatic plants or other algae species for pyridate.

The presented valid studies for the metabolite CL9673 for algae (Anabaena flos-aquae) of Hermes and Erk, 2013 and aquatic plants (Lemna gibba) of Grade, 1997 deliver only additional information from our point of view. There is no reliable information about the toxicity of pyridate itself to algae or aquatic plants. Page 135 point 4.5 Comparison with criteria for environmental hazards: Relating acute aquatic toxicity of pyridate the classification criteria according CLP (2nd ATP) should be LC50 ≤ 1 mg/L. Page 136 point 4.6 Conclusion on classification and labeling for environmental hazards: The substance is "pyridate" (instead of "mandestrobin") in the column about bioconcentration.
Dossier Submitter's Response
Response to comment on study by Grade (1998): The study by Grade (1998) was assessed to be valid in the addendum to the DAR for the first Annex I inclusion and the endpoint was included in the list of endpoints. Also for the renewal procedure the study was indicated to be valid and accepted during the peer review process. The coefficient of variation of sectional specific growth rate was no validity criterion at the time when the study was conducted. Generally, it is considered questionable to evaluate studies according to guidelines not available at the time of study performance. Response to comment on comparison with criteria for environmental hazards: Agreed: LC_{50} ≤ 1 mg/L Response to comment on conclusion on classification and labeling for environmental hazards: Agreed, this was a copy-paste error.
RAC's response
RAC agrees with the Dossier Submitter answer regarding the Grade (1998) study.

Date	Country	Organisation	Type of Organisation	Comment number
21.02.2017	France		MemberState	24
Comment received				
We agree with the classification proposal regarding environmental hazard				
Dossier Submitter's Response				
Noted				
RAC's response				
Noted.				

PUBLIC ATTACHMENTS
1. Comments to the CLH report on pyridate.docx [Please refer to comment No. 6, 13, 17, 21]