Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

pirimicarb (ISO); 5,6-dimethyl-2-dimethylamino-pyrimidin-4-yl N,N-dimethylcarbamate

EC number: 245-430-1
CAS number: 23103-98-2

CLH-O-0000001412-86-39/F

Adopted

04 December 2014

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON PIRIMICARB

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that some attachments received may have been copied in the table below. The attachments received have been provided in full to the dossier submitter and RAC.

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Substance name: pirimicarb (ISO); 5,6-dimethyl-2-dimethylamino-pyrimidin-4-yl N,N-dimethylcarbamate
CAS number: 23103-98-2
EC number: 245-430-1
Dossier submitter: United Kingdom

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
18/07/2014	Germany		Member State	1
Comment received				
The German CA supports the proposed classification and labelling for Primicarb. In addition we have two remarks.				
Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
Thank you for your comments. RAC also agrees with classification for carcinogenicity (Category 2) and skin sensitisation (Cat 1). Sub-categorisation for skin sensitisation (Cat. 1B), however, is not supported by RAC since the intradermal induction dose was above 1% and the possibility of response rates compliant with sub-category 1A cannot be completely excluded.				

Date	Country	Organisation	Type of Organisation	Comment number
21/07/2014	the Netherlands		Member State	2
Comment received				
We agree with the proposed classification.				
Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
Thank you for your comments. See response to comment number 1.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
10/07/2014	Switzerland	Syngenta	Company-Manufacturer	3
Comment received				

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Syngenta disagrees with the proposal for cancer classification. See attached document for rationale.

ECHA note: The attachment no.1 has been copied below.

Introduction

The CLH report contains a proposal for a Category 2 cancer classification, H351, based on limited evidence for lung, ovary, liver & mammary gland tumours in the mouse.

Syngenta do not believe this classification is warranted, for the following reasons:

General comments on effects seen at high doses in both the AP and C57 black mouse studies

Many of the pirimicarb studies were conducted some time ago, at high dose levels that may now generally be viewed as excessively high.

The AP mouse study was conducted at 0, 200, 400, 1600ppm in diet. The highest dose level of 1600ppm was well in excess of an MTD, based on an increase in female mortality rate, and body weight gain reduction of significantly more than 10% vs. controls (up to 37% in males & 42% in females). The mid dose level of 400ppm was considered to be an MTD in females, based on increased mortality and reduced body weight gain vs. controls (10% at week 92). Thus any findings at 1600ppm are considered to be potentially confounded by excessive toxicity, and are not likely to be relevant for classification & labelling. Even findings in females at 400ppm should be viewed with caution.

The C57 black mouse study was conducted at 0, 50, 200, 700ppm in diet. The highest dose rate of 700ppm exceeded an MTD in both sexes, particularly in females, with an 8% lower body weight by week 82, and a body weight gain reduction of more than 10% vs. controls (by week 82, 12% in males and 23% in females – see Table 1 below).

Table 1: Intergroup Comparison of Bodyweights in g (Selected Timepoints; Adjusted Mean Values Shown for Weeks 2-81)

Weeks	Dietary Concentration of Pirimicarb (ppm)							
	Males				Females			
	0 (control)	50	200	700	0 (control)	50	200	700
1	22.8	22.8	22.8	22.7	18.0	18.1	18.1	18.2
2	23.8	23.6	23.7	23.5**	19.3	19.3	19.3	19.2
8	27.4	26.7**	27.0	26.0**	23.3	23.2	23.0	22.5**
17	30.6	29.7**	30.2	28.9**	25.0	24.9	24.8	24.1**
33	32.9	31.7**	32.7	31.1**	26.4	26.3	26.1	25.6**
49	34.6	33.6**	34.5	32.8**	28.0	27.6	27.4*	26.5**
65	34.7	34.4	35.1	33.1**	28.4	28.3	28.2	26.7**
81	34.5	33.9	34.5	33.0**	28.9	28.9	28.7	26.6**
Gain weeks 1-81	11.7	11.1	11.7	10.3	10.9	10.8	10.6	8.4
Gain as % control		94.9	100	88.0		99.1	97.2	77.1

** Statistically significant difference from control group mean, 1% level (Student's t-test, 2-sided)
* Statistically significant difference from control group mean, 5% level (Student's t-test, 2-sided)

It is generally recognized that toxicological effects, including tumours, seen at very high doses in animal studies are not relevant to the risk assessment for human exposure at very much lower exposure levels. This concept is written into the CLP guidance:

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"In lifetime bioassays…. the highest dose needs to induce minimal toxicity, such as characterised by an approximately 10% reduction in body weight gain (maximal tolerated dose, MTD dose). The MTD is the highest dose of the test agent during the bioassay that can be predicted not to alter the animal's normal longevity from effects other than carcinogenicity.
Excessive toxicity, for instance toxicity at doses exceeding the MTD, can affect the carcinogenic responses in bioassays. Such toxicity can cause effects such as cell death (necrosis) with associated regenerative hyperplasia, which can lead to tumour development as a secondary consequence unrelated to the intrinsic potential of the substance itself to cause tumours at lower less toxic doses. Tumours occurring only at excessive doses associated with severe toxicity generally have a more doubtful potential for carcinogenicity in humans."
"If a test compound is only found to be carcinogenic at the highest dose(s) used in a lifetime bioassay, and the characteristics associated with doses exceeding the MTD as outlined above are present, this could be an indication of a confounding effect of excessive toxicity. This may support a classification of the test compound in Category 2 or no classification."

Lung Adenoma

The following table shows the lung adenoma incidence in the C57 black mouse:

Table 2: Incidence of pulmonary adenoma & carcinoma in C57BL mouse (Rattray, 1998)

ppm	0	50	200	700
Pulmonary adenoma (benign)				
MALE				
Total incidence	1/55	1/55	1/55	3/55
Total incidence %	1.8%	1.8%	1.8%	5.5%
Laboratory HCD range	1 - 4/55 1.8 - 7.3%			
FEMALE				
Total incidence	0/55	0/55	0/55	6/55
Total incidence %	0%	0%	0%	10.9%
Laboratory HCD range	0 - 2/55 0 - 3.6%			
Pulmonary carcinoma (malignant)				
MALE				
Total incidence	0/55	0/55	0/55	0/55
FEMALE				
Total incidence	0/55	0/55	0/55	0/55

The incidence in male mice is within the laboratory control range.

It is Syngenta's position that the higher incidence of benign lung adenomas in females at the high dose level in this study is not indicative of a carcinogenic potential for man, for the following reasons:

- In the Alderley Park mouse, the increased tumour incidence at the highest dose level was at an exposure level clearly exceeding the MTD, thus these effects are not considered relevant to classification.
- In the C57 black mouse, an increased incidence of benign lung adenomas was only seen at the highest dose level, and only in females.
- There is no evidence of a dose response.
- This dose level was considered to exceed an MTD (23% reduction in bodyweight gain), therefore apparent effects seen only at this dose level are not considered to be relevant to human exposure, and not relevant to classification.
- The incidence in the study is outside the limited laboratory control range, however the very low background incidence of lung adenoma amplifies what may be an isolated chance higher incidence in this high dose female group.
- There is no evidence of any pre-neoplastic lesions in the lung.
- All tumours were benign, with no progression to carcinoma.
- The relevance of this tumour type to humans is questionable, as the type II bronchio-alveolar adenomas seen in mice are not generally seen in man, and thus the mouse is not considered to be a good model for human lung cancer.

- Pirimicarb was demonstrated to be non-genotoxic in a wide range of *in vivo* and *in vitro* studies.
- In a modern study, there was no evidence that pirimicarb was carcinogenic in the rat.

Ovarian Papillary Cystadenoma in the Mouse

The following table shows the ovarian tumour incidence in the AP mouse:

The 1600 ppm dose level clearly exceeds an MTD, hence any apparent effects at this dose level should not be considered relevant to classification.

Table 3: Incidence of ovarian papillary cystadenoma in AP mouse (Sotheran, 1980)

ppm	0	0	200	400	1600
FEMALE					
Total incidence	0/55	0/55	1/58	3/55	3/56
Total incidence %	0%	0%	1.7%	5.5%	5.4%

It is Syngenta's position that the ovarian cystadenomas seen only in the Alderley Park mouse studies, are not likely to be treatment related, based on the following:

- There are only very limited control data for this tumour type for lifetime studies in the same strain of mouse (Swiss-derived AP) at the same laboratory (4 studies), which show historical control incidence of 0-1/60 (0-1.7%). Relatively recent historical control data (HCD) generated by Charles River Laboratories, reported a maximal incidence of 7.27% (range 1.54-7.27%) in the Swiss-derived CD-1 mice from 54 studies (Giknis and Clifford, 2005[1]).
- Although the incidence at the top two doses in this study is outside the very limited laboratory historical control range, it is well within the Charles River control range for an almost identical strain of mouse. In addition, the incidence is low, and there is no dose response, suggesting that this is unlikely to be an effect of treatment, and may just reflect a variable background incidence for this finding.
- The higher tumour incidence is only seen at dose levels which meet or exceed an MTD.
- The following observations further support the position that the higher incidence of ovarian cystadenoma in this study is most likely a reflection of the normal variation in the incidence of this tumour type:
  - Tumours in this study were all benign (and therefore did not metastasise) and unilateral. Treatment related tumours are usually bilateral, and malignant forms are usually present.
  - There were no associated non-neoplastic changes in the ovary, such as reduced follicles/oocytes, atrophy, increased interstitial cells, proliferation of ovarian surface epithelium, invagination of or down growths of ovarian surface epithelium or increase in cystic structures - which would be expected with a treatment related neoplastic effect in the ovaries. There were also no hyperplastic or preneoplastic changes of the surface epithelium which are almost invariably associated with chemical carcinogenesis in the ovary.
  - The occurrence of treatment associated ovarian lesions in rodent carcinogenicity studies is not common. When they do occur, the commonly observed tumours with treatment are granulosa cell tumours and tubular (tubulostromal) adenoma. Cystadenoma are generally not associated with treatment in mice.

Liver tumours

The following table shows the liver tumour incidence in the AP mouse:

The 1600ppm dose level clearly exceeds an MTD, hence any apparent effects at this dose level should not be considered relevant to classification.

[1] Giknis M and Clifford C (2005) Spontaneous Neoplastic Lesions in the Crl:CD-1(ICR) Mouse in Control Groups from 18 Month to 2 year Studies. Charles River Website: http://www.criver.com/files/pdfs/rms/cd1/rm_rm_r_lesions_crlcd_1_icr_mouse.aspx

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Table 4: Lifetime AP mouse study – liver tumours

ppm	0	0	200	400	1600	Historical contol range + 5 years
Hyperplastic nodules and benign tumours (type A)						Benign liver tumours
MALE						
Total incidence	3/58	9/59	5/59	9/58	15/57	0 – 13/60
Total incidence %	5.2%	15.3%	8.5%	15.5%	26.3%	21.7%
FEMALE						
Total incidence	1/58	2/59	3/57	6/58	4/59	0 – 2/60
Total incidence %	1.7%	3.4%	5.3%	10.3%	6.6%	0 – 3.3%
Nodules with morphological signs of malignancy (type B)						Malignant liver tumours
MALE						
Total incidence	4/58	6/59	13/59	8/58	17/57	0 – 11/61
Total incidence %	6.9%	10.2%	22%	13.8%	29.8%	0 – 18%
FEMALE						
Total incidence	2/58	0/59	3/57	3/58	5/59	0 – 5/60
Total incidence %	3.5%	0%	5.3%	5.2%	8.5%	0 – 8.3%

It is Syngenta's position that the liver tumour incidence in the AP mouse study is not a treatment related effect, for the following reasons:

- The incidence is high & variable across all groups, with no clear evidence of a dose response
- Although the incidence in some dose groups slightly exceeded the laboratory historical control, there are only a very limited number of historical control studies for comparison
- This pattern probably reflects the normal background incidence of liver tumours for this strain of mouse
- No liver tumours were seen in the rat or in the C57 black mouse

Mammary gland adenocarcinoma

The following table shows the mammary tumour incidence in the AP mouse:

The 1600ppm dose level clearly exceeds an MTD, hence any apparent effects at this dose level should not be considered relevant to classification.

Table 5: Lifetime AP mouse study – mammary gland adenocarcinoma

ppm	0	0	200	400	1600	Historical control range + 5 years
FEMALE						
Total incidence	0/56	0/58	1/57	1/57	4/57	0 – 3/59
Total incidence %	0%	0%	1.8%	1.8%	7%	0 – 5.1%

It is Syngenta's position that the mammary gland tumour incidence in the AP mouse study is not a treatment related effect, for the following reasons:

- The incidence at the highest dose is only just outside the limited laboratory historical control
- The highest dose is considered to exceed the MTD, therefore apparent effects seen only at this dose level are not considered to be relevant to human exposure
- Even at the highest dose level, the incidence probably reflects the normal background

incidence
- There were no similar mammary gland changes in the C57 black mouse.

Conclusion

Thus, when all the information of relevance to the assessment of the carcinogenic potential of pirimicarb is taken into consideration, the only potentially treatment related effect is the observation of a small increase in incidence of benign lung adenomas in female mice, a finding in a single species, strain, sex and tissue occurring at a maximally tolerated dose level, with a clearly identifiable threshold. This is insufficient evidence to provide even limited evidence of carcinogenicity, and thus pirimicarb should not be classified for this endpoint.

[End of attachment no. 1]

Dossier Submitter's Response

Thank you for providing these comments. The information above and in the CLH report should be considered further by RAC.

RAC's response

Thank you for your comments.

RAC agrees that the highest dose (1600 ppm) in Alderley Park Swiss-derived mice study exceeded the MTD. Since in this study other methodological drawbacks are recognised as well (low survival rates without survival-adjustment for tumour incidence; mouse strain with high and variable spontaneous incidence of lung tumours; limited relevant historical control data) it is not considered reliable and provides supportive evidence only.

On the other hand, the top dose in the C57 black mice study is not considered to induce excessive toxicity. Namely, Pirimicarb treatment did not affect mortality rate in any exposed group and other effects were not regarded by RAC as indicators of severe toxicity (a slight increase in the incidence of eye discharge and subcutaneous masses was not related to adverse histopathological changes; an increase in relative liver weight was not associated with pathological microscopic changes; changes in red blood cells parameters were not indicative of anaemia; increased platelet count was inside the wide range found in healthy mice and thrombotic events were not reported; lymphoid accumulation in the lungs and spleen pigmentation are common non-neoplastic findings in black mouse). Nevertheless, even in the case that the top dose is considered to be above the MTD, classification remains an option according to the CLP Guidance on the application of the CLP criteria (version 4.0, November 2013): "*If a test compound is only found to be carcinogenic at the highest dose(s) used in a lifetime bioassay, and the characteristics associated with doses exceeding the MTD as outlined above are present, this could be an indication of a confounding effect of excessive toxicity. This may support a classification of the test compound in Category 2 or no classification*."

The absence of dose-response pattern in lung adenoma incidence in C57 black mice females does not *per se* exclude the possibility to classify Pirimicarb as a carcinogen in category 2 (Carc. 2). As mentioned earlier, according to the CLP Guidance tumorigenic potential that is observed only at the highest dose (even exceeding MTD) "*may support a classification of the test compound in Category 2 or no classification*". Regarding the findings observed in only one sex, the CLP Guidance states that "*There may be cases where tumours are only observed in one sex... A default position is that such tumours are still evidence of carcinogenicity and should be evaluated in light of the total tumorigenic response...*".

Pre-neoplastic lesions, such as foci of cell proliferation, are not always observed in tumourigenic processes. For example, in humans "*although the sequential pre-neoplastic changes have been defined for centrally arising squamous carcinomas of the lung, they have been poorly documented for the other major forms of lung cancers...*" (Wistuba II, Gazdar AF. Lung cancer preneoplasia. Annu Rev Pathol. 2006; 1:331-48). Also, in the present study in C57 black mice, no cell proliferation of alveolar/bronchiolar epithelium was reported either at interim or terminal kills, although an increased incidence of lung adenoma was found.

According to the CLP Guidance, benign tumours could also be relevant for classification, usually in Category 2 since "*The induction of only benign tumours usually provides a lower strength of evidence for carcinogenicity than the induction of malignant tumours and will usually support Category 2...*"

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The relevance of mice lung adenoma for humans could not be dismissed since no mechanistic data on Pirimicarb carcinogenicity were provided, and, although rarely, benign (alveolar adenoma) and malignant (bronchioloalveolar carcinoma) tumours that arise from type II pneumocytes occur in humans as well.

Date	Country	Organisation	Type of Organisation	Comment number
18/07/2014	Belgium		Member State	4

Comment received

We agree with the proposal to classify for carcinogenicity in category 2 based on limited evidence:
• Many tumours incidences within the range of the historical control data (brain astrocytoma in rats, mammary gland fibroadenoma in rats, stromal cell sarcoma in rats, ..).
• Treatment related tumours only in one species (mice).
• Many tumour incidences only exceeded the historical control range at doses above the MTD (pulmonary adenoma in mice, mammary gland adenocarcinoma in mice).
Besides, none data dismiss the relevance of these tumours for humans. Then a classification in category 2 (H351) is warranted due to the limited evidence.

Dossier Submitter's Response

Thank you for your comments.

RAC's response

Thank you for your comments. RAC also agrees with classification for carcinogenicity Cat 2 based on increased incidence of lung adenomas in female C57 black mice and the absence of mechanistic data that could dismiss the relevance of lung adenoma for humans. A single incidence of benign keratinising squamous epithelioma in C57 black mice females at the highest dose is considered to be supportive of a treatment-related effect in the lungs. Also, an increased incidence of lung adenomas, liver tumours and ovarian papillary cystadenoma in Alderley Park Swiss derived mice in a study with low survival rates without survival-adjustment for tumour incidence and in a strain with high and variable spontaneous incidence of lung tumours, are considered as supportive evidence for the carcinogenic potential of Pirimicarb.

Date	Country	Organisation	Type of Organisation	Comment number
21/07/2014	the Netherlands		Member State	5

Comment received

Agree.

Dossier Submitter's Response

Thank you for your comments.

RAC's response

Thank you for your comments. See response to comment number 4.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
07/07/2014	Finland		Member State	6

Comment received

The Finnish CA supports the proposed classification according to CLP regulation Acute Tox. 3; H301 and Acute Tox. 3; H331 for Pirimicarb.

Dossier Submitter's Response

Thank you for your comments.

RAC's response

Thank you for your comments. RAC also agrees with the proposed classification for acute toxicity.

Date	Country	Organisation	Type of Organisation	Comment number
18/07/2014	Belgium		Member State	7

Comment received

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON PIRIMICARB

We support the classification for the acute toxicity in category 3 based on:
• Via the oral route : the study in rats (Lee & Connolly, 1995) reveals a LD50 of 152 and 142 mg/kg bw, respectively for males and females. These results are within the range of the category 3 H301 (>50 and ≤300 mg/kg bw).
• Via the inhalation route: the study in rats (Parr-Dobrzanski, 1994) indicate a LC50 of 0.948 and 0.858 mg/l/4h, respectively for males and females. These results are within the range of the category 3H331 (>0.5 and ≤1 mg/l/4h).

Dossier Submitter's Response

Thank you for your comments.

RAC's response

Thank you for your comments. RAC also agrees with the proposed classification for acute toxicity.

Date	Country	Organisation	Type of Organisation	Comment number
21/07/2014	the Netherlands		Member State	8

Comment received

Agree.

Dossier Submitter's Response

Thank you for your comments

RAC's response

Thank you for your comment. RAC also agrees with the proposed classification for acute toxicity.

Skin Sensitization

Date	Country	Organisation	Type of Organisation	Comment number
07/07/2014	Finland		Member State	9

Comment received

The Finnish CA supports the proposed classification as Skin Sens. 1B; H317 for Pirimicarb. However, the description of the guinea pig maximisation test in the CLH proposal could be improved. Was a pilot study conducted to determine the appropriate test substance concentrations for the induction and challenge exposure? And was any skin irritation observed during the induction phase?

Dossier Submitter's Response

Thank you for your comments. The concentrations of the test substance used during induction and challenge phases were selected based on a range finding study. During the study, scattered mild or moderate diffuse redness was observed in response to the challenge application with 75% w/v dilution of pirimicarb in corn oil (6/19 animals). Scattered mild redness to intense redness and swelling was seen in response to the 30% w/v dilution (9/19 animals). No skin reactions were observed in the control animals.

RAC's response

Thank you for your comments.
RAC also agrees with classification for Skin sensitisation Cat 1. Sub-categorisation for skin sensitisation (Cat. 1B), however, is not supported by RAC since the intradermal induction dose was above 1% and the possibility of response rates compliant with sub-category 1A cannot be completely excluded.

Date	Country	Organisation	Type of Organisation	Comment number
18/07/2014	Belgium		Member State	10

Comment received

We agree with the classification proposal for the skin sensitisation. The guinea pig study (Rattray and Leah, 1990), indicates a positive response in 47% and in 32% of the tested animals challenged respectively with 30% and 75%. These positive responses were observed following an intradermal induction of 3%. These results fulfil the criteria of the category 1B (≥30% responding at >1% intradermal induction dose). The percentage of response doesn't exceed 60% despite an induction dose of 3%. Then a classification in category 1A is unlikely. Therefore, the sub-classification in category 1B (H317) is supported.

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Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
Thank you for your comments. See response to comment number 9.				
Date	**Country**	**Organisation**	**Type of Organisation**	**Comment number**
21/07/2014	the Netherlands		Member State	11
Comment received				
Agree.				
Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
Thank you for your comment. See response to comment number 9. RAC also agrees with classification for skin sensitisation Cat 1. Sub-categorisation for skin sensitisation (Cat. 1B), however, is not proposed by RAC since the intradermal induction dose was above 1% and the possibility of response rates compliant with sub-category 1A cannot be completely excluded.				

Specific target organ toxicity – repeated exposure

Date	**Country**	**Organisation**	**Type of Organisation**	**Comment number**
07/07/2014	Finland		Member State	12
Comment received				
The UK CA does not propose classification of Pirimicarb for STOT-RE due to hematological effects. The justification for this is that hematological effects and anemia observed in dog studies are considered inconsistent, and only small changes in hematological parameters (no anemia) were observed in rat studies. We do not fully agree with this. Although severity of the effects varied between different studies (from severe anemia and death to small hematological effects) hematological effects were consistently observed in all studies reported. The acute neurotoxicity caused by inhibition of acetylcholinesterase is apparently the prime cause of mortalities in acute toxicity studies. In accordance with the guidance, to avoid double classification for the same toxic effects, the UK CA proposes not to classify Pirimicarb for STOT-SE (pages 15 and 17), since neurotoxic effects are already covered by acute toxicity classification. The DS also does not propose classification of Pirimicarb for STOT-RE for neurotoxic effects. We think that classification of Pirimicarb for STOT-RE due to neurotoxic effects should be considered by RAC. The DS discusses that reductions in acetylcholinesterase activities observed in repeated dose toxicity studies were transient due to reversible nature of the inhibition and that the effects did not accumulate in severity during the course of the study. Thus, the effect would be better characterized as acute or single dose effect (acute toxicity or STOT-SE).Yet, reductions of erythrocyte, brain and plasma acetylcholinesterase activities were observed consistently in repeated toxicity studies, although sampling was (in some studies) done after inhibition of the enzyme was possibly reversed. In some repeated toxicity studies erythrocyte and brain acetylcholinesterase activities were even reduced to adverse levels and also serious neurological signs of toxicity were observed. According to CLP all significant health effects that can impair function, reversible and irreversible, immediate and/or delayed are included in STOT-RE (Annex I 3.9.1.1.). The assessment should take into consideration not only significant changes in a single organ or biological system but also generalized changes of a less severe nature involving several organs (Annex I 3.9.1.4.). Moreover according to guidance the purpose of STOT-RE is to identify the primary target organ(s) of toxicity for inclusion in the hazard statement. The primary target of Pirimicarb toxicity is nervous system i.e. acetylchlolinesterase inhibition. Although the inhibition caused by carbamate insecticides is reversible, not irreversible as it is in the case of more toxic organophosphate insecticides, this mechanism is known to be relevant for humans. In open literature carbamate insecticides have been reported to cause poisonings to humans. In conclusion, for these reasons the Finnish CA is of the opinion that classification of Pirimicarb for STOT-RE due to neurotoxic effects (inhibition of acetylcholinesterase) should be considered by RAC. Moreover, classification of Pirimicarb for STOT-RE due to hematological effects should be considered.				

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Dossier Submitter's Response

Thank you for your comments and we note your conclusion on the classification. We have provided all available and relevant information regarding STOT-RE in support of the proposed classification for carcinogenicity. However, as the substance already has an entry in Annex VI of CLP and the classification was previously agreed at the EU level, this hazard class was not formally proposed as agreed with the ECHA Secretariat.

RAC's response

Thank you for your comments. As the DS explained in their response and in the CLH dossier, the STOT RE hazard class was not formally proposed for evaluation, and the data on repeated dose toxicity (as well as for mutagenicity) were only provided as support for the analysis of carcinogenicity.

Date	Country	Organisation	Type of Organisation	Comment number
17/07/2014	France	ANSES		13

Comment received

Specific target organ toxicity repeated exposure category 2 (STOT RE cat 2). Page39
The CLP guidance on the application of CLP criteria, listed several health effects for which a classification for STOT-RE for haemolytic anemia is warranted (refer to point 3.9.2.5.2 Hematotoxicity). For a classification, it is sufficient that only one of these criteria is fulfilled. Among these criteria we have:
- Morbidity or death resulting from repeated or long-term exposure.
- Any consistent and significant adverse effect in clinical biochemistry, haematology or urinalysis parameters; Reduction in Hb at ≥ 20%.

Considering the above criteria and based on the following toxicological data on Pirimicarb, France thinks that a classification as Specific target organ toxicity repeated exposure category 2 (STOT RE cat 2) is required.

In fact, the review of all available data on Pirimicarb indicated that the substance induce Immune-hemolytic anemia on dog described as a compound dependent haemolytic anaemia of the 'penicillin type. In the mechanistic study (Garner et al, 1972), analysis of serum proteins showed that exposure to Pirimicarb produced an antibody reaction in the sera of the two anaemic dogs (accompanied by the absence of a reaction in the 2 unaffected dogs and 20 untreated dogs).It was shown that the antibody and the antigenicity of the red cells were related in time to the administration of Pirimicarb. The antibody was not present in the preexperimental serum samples and the red cell possessed the appropriate antigen only when the dogs were receiving Pirimicarb. Withdrawal of Pirimicarb was followed by a marked decline in antibody titre and circulating red cells did not react with specific antiglobulin serum. Characterisation of the antibody showed it to be an immune type (probably IgG).

Immune-hemolytic anemia is describe as being an idiosyncratic phenomenon (largely) and is thus infrequently detected in preclinical study. When it is observed, there are typically one or two animals affected, and they may or may not be in the high-dose group (Principles and methods of toxicology.4th edition. 2001)

In the 90-day dietary study in the beagle dog (Griffiths & Conning, 1968), 1/4 male of the top dose group died (week 10, 25 mg/kg bw/day) exhibiting anaemia (↓ 66.3% Hb). At post-mortem examination of the bone marrow, marked erythropoietic hyperplasia, delayed maturation of the red cell series and an increase in the number of megaloblasts was observed. In addition, anaemia was observed in 1/4 females in the 25 mg/kg bw/day group (↓43.2% Hb) and 1/4 females in the 10 mg/kg bw/day group (↓63.1% Hb). Anaemia was not observed in any of the other dogs, but examination of terminal blood films revealed an increased erythrocyte diameter and an increase in the number of circulating erythroblasts (at 10 mg/kg bw/day in individual dogs). Investigation of the bone marrow in all animals revealed an increase in megaloblasts (Males at 10 mg/kg bw/day and females in all treatment groups), lymphocytes (males at 10 mg/kg bw/day) and early normoblasts (males at 25 mg/kg bw/day).

In the 1-year study in the beagle dog (Horner, 1998), 1/4 female of the top dose group (25 mg/kg bw/day) was sacrificed (week 36) due to moderately severe anaemia (a reduction in red blood cell count (↓52.1%), haemoglobin (↓53.7%), haematocrit (↓42.0%) at week 13). Histopathological and

bone marrow changes for this female were consistent with an increase in red blood cell breakdown and included an increase in haemosiderin deposition, increased bone marrow cellularity and a significant decrease in the myeloid:erythroid ratio (indicative of increased erythropoietic activity). No signs of anaemia were observed in the haematological and bone marrow investigations for the other treated animals. However, an increase in extramedullary haemopoiesis of the spleen (25 mg/kg bw/day: 1/4 M & 1/3 F and 10 mg/kg bw/day: 1/4 F) and an increase in haemosiderin deposition of the liver (25 mg/kgbw/day: 3/4 M) were observed, which may indicate that the ability of these individuals to cope with the level of red blood cell destruction was being challenged.

In the third (2-year) study conducted with beagle dogs, no effects on haematology, were observed. However, the dose selection in this study was questionable (top dose of 4 mg/kg bw/day). At the top dose there was a slight increase in the erythroid: myeloid ratio in the bone marrow, which could be an adaptive response to increased red blood cell haemolysis.

In an additional 16-week study in foxhounds, anaemia and reticulocytosis were associated with treatment at 50 mg/kg/day, with a reduction in haemoglobin, packed cell volume and erythrocyte count and an increase in reticulocytes. Changes in bone marrow were associated with an increase in the number of normoblasts from week 9 and a tendency towards suppression of bone marrow activity (hypoplasia). A marked increase in absolute and relative spleen weight was observed in all treated females when compared with the control female. Even if this study was not performed according to Standard Test Guidelines and the lack of historical control data for foxhounds; the observed haematological changes appear to be similar to those observed in the beagle dog.

Dossier Submitter's Response

Thank you for your comments and we note your conclusion on the classification. We have provided all available and relevant information regarding STOT-RE in support of the proposed classification for carcinogenicity. However, as the substance already has an entry in Annex VI of CLP and the classification was previously agreed at the EU level, this hazard class was not formally proposed as agreed with the ECHA Secretariat.

RAC's response

Thank you for your comments. See response to comment number 12.

Date	Country	Organisation	Type of Organisation	Comment number
18/07/2014	Germany		Member State	14

Comment received

Pages 20 – 39: Even though effects on red blood cells (including those on bone marrow) in particular in dogs (but occasionally also seen in rats) were not consistent throughout the studies, it seems that anaemia is a treatment-related effect occurring at rather low doses at least in susceptible animals. In addition, occurrence of neurological signs in dogs might also trigger classification. Thus, in line with the EU evaluation as reflected in the Scientific Report of EFSA (2005), we consider a classification for STOT-RE (cat. 2, H373) as appropriate. Apart from that, the German CA supports all other proposals for classification and labelling for health effects made by the English CA.

Dossier Submitter's Response

Thank you for your comments and we note your conclusion on the classification. We have provided all available and relevant information regarding STOT-RE in support of the proposed classification for carcinogenicity. However, as the substance already has an entry in Annex VI of CLP and the classification was previously agreed at the EU level, this hazard class was not formally proposed as agreed with the ECHA Secretariat.

RAC's response

Thank you for your comments. See response to comment number 12.

Hazardous to the aquatic environment

Date	Country	Organisation	Type of Organisation	Comment number
07/07/2014	Finland		Member State	15

Comment received

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON PIRIMICARB

The Finnish CA supports the proposed classification Aquatic Acute 1; H400, M=10 and Aquatic Chronic 1; H410, M=100 for Pirimicarb.
The aquatic ecotoxicity studies were described very shortly in the CLH proposal. This was done because the substance has been already reviewed under Directive 91/414/EEC. However, we think that those key studies on which the classification proposal is based on might have been described in more detailed in the CLH proposal.

Dossier Submitter's Response

Thank you for the comments. We believe that sufficient information has been provided in the CLH report to allow for a decision on the classification and labelling. We will of course provide further information to RAC should they require any additional clarification on specific issues.

RAC's response

A general lack of detailed information on studies is noted also by RAC.

Date	Country	Organisation	Type of Organisation	Comment number
18/07/2014	Belgium		Member State	16

Comment received

Based on the results of the aquatic toxicity test on the most sensitive species (Daphnia magna with 48h EC50 = 0.017mg/l and 21d NOEC = 0.0009mg/l), the fact that the substance is considered as not rapidly degradable it is justified to classify, following the classification criteria of the regulation 1272/2008, as Aquatic acute 1, H400 and Aquatic chronic 1, H410. Furthermore, the substance shows low potential to bioaccumulate.

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 could be assigned and an M-factor for chronic toxicity of 100 (not rapidly degradable substance and toxicity band between 0.0001mg/l and 0.001 mg/l).

In conclusion: we agree with the proposed environmental classification by UK CA.

General comment:
Aquatic toxicity: More details on the materials and methods (species life stage, test conditions, test design,…) as well as on the observations (control, abnormal behaviour,…) at least for the key studies, would have been preferable.

Dossier Submitter's Response

Thank you for the comments. We believe that sufficient information has been provided in the CLH report to allow for a decision on the classification and labelling to be taken. We will of course provide further information to RAC should they require any additional clarification on specific issues.

RAC's response

A general lack of detailed information on studies is noted also by RAC.

Date	Country	Organisation	Type of Organisation	Comment number
18/07/2014	Germany		Member State	17

Comment received

Page 68, point 5.4.1.1 short-term toxicity to fish:
There exist additional valid data for acute fish toxicity for Pirimicarb (97.7 % purity):
1) Flow-through study with Lepomis macrochirus LC50 (96h) of 55 mg/L nominal (Hill,R.W.,1978; Report No. BL/B/1893)
2) Flow through study with Oncorhynchus mykiss LC50 (96h) of 29 mg/L nominal (Hill,R.W.,1978; Report No. BL/B/1896)
Because aquatic invertebrates (Daphnia magna) are the most sensitive species for Pirimicarb with EC50(48h) of 0.017 mg/L nominal, the additional data have no influence on proposed classification and labeling of Pirimicarb.

Dossier Submitter's Response

Thank you for the comments. We believe that sufficient information has been provided in the CLH report to allow for a decision on the classification and labelling to be taken and the additional information will not influence the proposed classification. We will of course provide further info to

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON PIRIMICARB

RAC should they require any additional clarification on specific issues.				
RAC's response				
RAC noted the additional data for acute fish toxicity for Pirimicarb, and agrees with MS that the information provided has no influence on proposed classification and labelling.				
Date	**Country**	**Organisation**	**Type of Organisation**	**Comment number**
21/07/2014	the Netherlands		Member State	18
Comment received				
Agree, also with the proposed M factors.				
Dossier Submitter's Response				
Thank you for the comments.				
RAC's response				
Noted.				

ATTACHMENTS RECEIVED: 1

1. *Pirimicarb CLH report - Syngenta Response to Public Comments July 2014.docx. Comment is copied under comment no.3.*