Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

pirimiphos-methyl (ISO); *O*-[2-(diethylamino)-6-methylpyrimidin-4-yl] *O*,*O*-dimethyl phosphorothioate

EC Number: 249-528-5
CAS Number: 29232-93-7

CLH-O-0000001412-86-247/F

Adopted

30 November 2018

30 November 2018

CLH-O-0000001412-86-247/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **pirimiphos-methyl (ISO); *O*-[2-(diethylamino)-6-methylpyrimidin-4-yl] *O*,*O*-dimethyl phosphorothioate**

EC Number: **249-528-5**

CAS Number: **29232-93-7**

The proposal was submitted by **United Kingdom** and received by RAC on **30 January 2018.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

United Kingdom has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **12 February 2018**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **13 April 2018**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: Marja Pronk

Co-Rapporteur, appointed by RAC: Pietro Paris

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **30 November 2018** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	015-134-00-5	pirimiphos-methyl (ISO); *O*-[2-(diethylamino)-6-methylpyrimidin-4-yl] O,O-dimethyl phosphorothioate	249-528-5	29232-93-7	Acute Tox. 4* Aquatic Acute 1 Aquatic Chronic 1	H302 H400 H410	GHS07 GHS09 Wng	H302 H410			
Dossier submitters proposal	015-134-00-5	pirimiphos-methyl (ISO); *O*-[2-(diethylamino)-6-methylpyrimidin-4-yl] O,O-dimethyl phosphorothioate	249-528-5	29232-93-7	**Modify**: Acute Tox. 4 **Add**: STOT RE 1 **Retain**: Aquatic Acute 1 Aquatic Chronic 1	**Add**: H372 (AChE inhibition) **Retain**: H302 H400 H410	**Retain** GHS07 GHS09 **Add** GHS08 **Modify** Dgr	**Add**: H372 (AChE inhibition) **Retain**: H302 H410		**Add**: oral: ATE = 1414 mg/kg bw M=1000 (acute) M=1000 (chronic)	
RAC opinion	015-134-00-5	pirimiphos-methyl (ISO); *O*-[2-(diethylamino)-6-methylpyrimidin-4-yl] O,O-dimethyl phosphorothioate	249-528-5	29232-93-7	**Modify**: Acute Tox. 4 **Add**: STOT RE 1 **Retain**: Aquatic Acute 1 Aquatic Chronic 1	**Add**: H372 (nervous system) **Retain**: H302 H400 H410	**Retain** GHS07 GHS09 **Add** GHS08 **Modify** Dgr	**Add**: H372 (nervous system) **Retain**: H302 H410		**Add**: oral: ATE = 1414 mg/kg bw M=1000 (acute) M=1000 (chronic)	
Resulting Annex VI entry if agreed by COM	015-134-00-5	pirimiphos-methyl (ISO); *O*-[2-(diethylamino)-6-methylpyrimidin-4-yl] O,O-dimethyl phosphorothioate	249-528-5	29232-93-7	Acute Tox. 4 STOT RE 1 Aquatic Acute 1 Aquatic Chronic 1	H302 H372 (nervous system) H400 H410	GHS07 GHS08 GHS09 Dgr	H302 H372 (nervous system) H410		oral: ATE = 1414 mg/kg bw M=1000 (acute) M=1000 (chronic)	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Pirimiphos-methyl is an active substance in the meaning of Regulation (EU) No 1107/2009 and is used as a broad-spectrum insecticide for use in grain stores and related industrial outlets.

This substance has an existing entry in Annex VI of the CLP regulation. This CLH proposal aims at modifying the existing classification based on data submitted as part of the pesticide renewal process (partly old, partly new data when compared to the original application).

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

The scope for acute toxicity was limited to the oral route, to address the current minimum classification.

In a study according to OECD TG 401 and GLP (Anon. 1999), Alpk:AP$_f$SD rats (5/sex/dose) were administered 500, 1 000 or 2 000 mg/kg bw of pirimiphos-methyl (91.7 % pure) in corn oil via gavage. Clinical signs considered to be treatment-related (including piloerection, urine staining and neurological signs such as tip toe gait, salivation and upward curvature of the spine) were seen in all treatment groups with a dose-related increase in severity. No deaths were observed at 500 and 1 000 mg/kg bw, but at 2 000 mg/kg bw all rats were killed in extremis on day 2-3. The acute oral LD_{50} was determined at 1 414 mg/kg bw. Classification in category 4 was proposed by the DS as the LD_{50} is within the limits of 300–2 000 mg/kg bw for category 4, with an oral ATE of 1414 mg/kg bw.

Comments received during public consultation

The proposed classification was supported by two MSCAs.

Assessment and comparison with the classification criteria

The oral LD_{50} of 1 414 mg/kg bw determined in rats lies within the numeric criteria for Acute Tox. 4 (300–2 000 mg/kg bw). Therefore, RAC supports the DS proposal for **Acute Tox. 4; H302**, with an **ATE of 1 414 mg/kg bw**.

RAC evaluation of specific target organ toxicity– repeated exposure (STOT RE)

Summary of the Dossier Submitter's proposal

The repeated dose oral toxicity of pirimiphos-methyl has been investigated in a number of studies in rats, mice and dogs. These include a 28-day, 90-day and 2-year study in the rat, a 90-day and 78-week study in the mouse and a 2-year study in the dog. Information is also available

from an oral 2-generation and an oral sub-chronic neurotoxicity study in rats. For the dermal route a 3-week study in the rabbit is available.

The most significant effect observed throughout all these studies was acetylcholinesterase inhibition, measured in plasma, erythrocytes and brain (see short study summaries below, with more details presented in Table S1 under Supplemental information). In all of the studies, there were no consistent evidence of effects on clinical chemistry, haematology or at gross or microscopic examinations, other than those related to acetylcholinesterase inhibition.

Rat, 28-day (Anon., 1975; pre-dating OECD TG and GLP)

In a 28-day dietary study in rats, no adverse effects were observed up to and including the highest dose of 6 mg/kg bw/day (brain cholinesterase activity was significantly reduced at the high dose (11-13 %) but not to levels > 20 %).

Rat, 90-day (Anon., 1970; pre-dating OECD TG and GLP)

In a 90-day dietary study in rats, a reduction in female body weight gain of approximately 20 % was observed at 7 and 32 mg/kg bw/day. At these doses, females also showed a reduction in brain cholinesterase activity of 20 % or more which did not recover within 4 weeks. Erythrocyte cholinesterase activity was reduced more than 20 % in males and females at 32 mg/kg bw/day from week 2 and in females at 7 mg/kg bw/day from week 6. Only in females at 32 mg/kg bw/day the reduction did not fully recover within 4 weeks.

Rat, 92-day neurotoxicity study (Anon., 1995a; according to OECD TG 424 and GLP)

In a 92-day dietary neurotoxicity study in rats, a reduction in erythrocyte cholinesterase activity of more than 20 % was observed from week 3 at the highest dose of 21.1 (males) or 24.7 (females) mg/kg bw/day. The same dose also induced a reduction in brain cholinesterase activity of more than 20 % in both sexes. No effects were observed at the next lower dose level of approximately 2 mg/kg bw/day and below.

Rat, 2-generation study (Anon., 1995; according to OECD TG 416 and GLP)

In a dietary 2-generation study in rats, a reduction in female body weight gain of approximately 10 % was observed at the highest dose of 12 (F_0) and 15 (F_1) mg/kg bw/day. Erythrocyte cholinesterase activity was reduced at some time points at 1 (males only), 3/4 (F_0/F_1) and 12/15 (F_0/F_1) mg/kg bw/day. Brain cholinesterase activity was reduced by more than 20 % in females at 3 (F_0) and 4 (F_1) mg/kg bw/day and above.

Rat, combined chronic and carcinogenicity study (Anon, et al., 1974; pre-dating OECD TG and GLP)

In a dietary chronic (2-year) study in rats, a small increase in severe fatty vacuolation of the liver was observed in females at the highest dose of 12.6 mg/kg bw/day (17 % versus 7 % in controls). At the same dose, also a small increase in cystic vacuolation of the epididymis was observed (4/42 males versus 0 in controls). Erythrocyte cholinesterase activity was reduced by more than 20 % at the highest dose in both males (from week 12) and females (from week 2), but was reversible within 4 weeks. Brain cholinesterase activity was reduced by more than 20 % at 2.1 (males only) and 12.6 mg/kg bw/day. At the highest dose this reduction was not fully reversible within 4 weeks, although the level of inhibition diminished to < 20 %.

Mice, 90-day (Anon., 1996; according to OECD TG 408 and GLP)

In a dietary 90-day study in mice, the highest dose group (178/284 mg/kg bw/day m/f) was terminated after week 2 due to severe toxicity. Clinical signs (cyanosis, piloerection and hunched

posture), slight reductions in body weight and reduced food consumption were observed at the next lower dose of 63/80 mg/kg bw/day (m/f) but not at lower doses. Erythrocyte cholinesterase activity was reduced by more than 20 % from week 1 at 2 (males) and 9 (females) mg/kg bw/day and above. In females at 3 mg/kg bw/day such a reduction was observed from week 3 onwards. Brain cholinesterase activity was reduced in all groups, but by more than 20 % only from 20/26 mg/kg bw/day (m/f).

Mice, combined chronic and carcinogenicity study (Anon. et al., 1996; according to OECD TG 451 and GLP)

In a dietary chronic (78-week) study in mice, the highest dose was reduced from 400 ppm (72 mg/kg bw/day) to 300 ppm (57 mg/kg bw/day) after week 1 due to body weight loss. An initial increased level of early deaths was evident at 36 and 57 mg/kg bw/day in males; likely causes of the deaths were anticholinesterase effects, nephropathy or urinary bladder obstruction. Clinical signs showed a dose-related pattern of severity and incidence at 36 and 57 mg/kg bw/day and included pilo-erection, dark eyes, hunched posture, cyanosis and agitation, with tremors additionally noted at 57 mg/kg bw/day. In mice from the 36 and 57 mg/kg bw/day groups, dying or sacrificed during the study (but not in animals surviving to 78 weeks), there was an increased incidence of thymic lymphoid atrophy, a finding which appeared to be associated with poor general condition. A reduction in cholinesterase activity of more than 20 % was observed in erythrocytes from the lowest tested dose of 9 mg/kg bw/day. In brain this reduction was mainly seen from 36 mg/kg bw/day, but males at 9 mg/kg bw/day also showed a reduction of more than 20 % at the interim sacrifice after 52 weeks.

Dogs, 2-year (Anon., 1973; pre-dating OECD TG and GLP)

In a 2-year study in dogs (4/sex/dose) using oral capsules, brain cholinesterase activity was significantly reduced at 0.5, 2 and 10 mg/kg bw/day, but by more than 20 % only at the highest dose. Erythrocyte cholinesterase activity was reduced by more than 20 % at 2 (from week 25/26) and 10 mg/kg bw/day (from week 1). Clinical signs of toxicity were mainly observed in the top dose group and included loose faeces and vomiting (within half an hour of dosing). Loss of appetite and body condition occurred from week 3 in 2 males at the top dose level and resulted in a loss of weight. However, body weight gain improved in these two animals from week 7 or 10.

Dermal study in rabbits (Anon., 1980; pre-dating OECD TG and GLP)

In a 3-week dermal study in rabbits (5/sex/dose, treatment on 5 days/week), erythrocyte cholinesterase activity was reduced above 20 % in females at all dose levels (4, 40 and 400 mg/kg bw/day) and in males at 400 mg/kg bw/day. Brain cholinesterase activity varied greatly between animals and groups. Mortalities (cause unknown) were seen in 3 top dose animals, 1 mid-dose animal and 1 low dose animal but not in controls.

In evaluating the effects on acetylcholinesterase inhibition in the available studies, the DS referred to the recommendations of the WHO JMPR, stating that the inhibition of brain cholinesterase activity and clinical signs are considered to be the primary endpoints of concern in toxicological studies on compounds that inhibit acetylcholinesterases. Inhibition of erythrocyte acetylcholinesterase is also considered to be an adverse effect, insofar as it is used as a surrogate for brain and peripheral nerve acetylcholinesterase inhibition, when data on the brain enzyme are not available. In line with these recommendations, the DS considered a significant inhibition of brain and erythrocyte acetylcholinesterase by 20 % or more to represent a clear toxicological adverse effect, even when not accompanied by clinical signs. As inhibition of acetylcholinesterase leads to acetylcholine accumulation, hyperstimulation of nicotinic and muscarinic receptors and

disrupted neurotransmission, the DS further considered the adverse effects to warrant classification for STOT RE, if occurring at levels at or below the cut-off for classification.

When looking at the oral data available on pirimiphos-methyl, cholinesterase activity inhibition in the brain or in erythrocytes by more than 20 % was observed in all studies with rats, mice and dogs (at almost all dose levels tested), with the exception of the 28-day rat study. There was also some evidence of acetylcholinesterase inhibition in the dermal rabbit study. The inhibition was dose dependent but rarely increased with time. It was not always found to be (fully) reversible. Clinical signs were only observed in dogs (at 10 mg/kg bw/day) and mice (at dose levels from 36 mg/kg bw/day), at the higher dose levels tested. No clinical signs were observed in rats tested up to 32 mg/kg bw/day in the repeated dose studies. In contrast, in acute oral studies in rats, clinical effects were observed at doses ranging from 500 to 2000 mg/kg bw. The DS assumed that these effects as well as the observed mortality at 2000 mg/kg bw were caused by cholinesterase activity inhibition. Whilst recognizing that the effects in the repeated dose studies could also be an acute or single dose effect, the DS noted that the effects on cholinesterase activity occurred at much lower dose levels (> 100 fold less) in the repeated dose studies as compared to the acute studies. Given this difference, the DS concluded that the toxicity did not occur at a "similar dose" and that classification only with acute toxicity, category 4, would not appear to be sufficient.

According to the DS, the lowest levels at which cholinesterase inhibition above 20 % occurred was approximately 3-7 mg/kg bw/day in rats (as observed in oral 90-day studies), 2/3 mg/kg bw/day in mice (in oral 90-day study), 2 mg/kg bw/day in dogs (in oral 2-year study) and 40 mg/kg bw/day in rabbits (in dermal 3-week study). Since these levels in rats, mice and rabbits are below the cut-off for classification with STOT RE 1 (10 mg/kg bw/day for an oral 90-day study, 85 mg/kg bw/day for a dermal 3-week study), classification with STOT RE 1 was proposed. No specification of the route was suggested; the suggested target organ was "inhibition of acetylcholinesterase activity".

Comments received during public consultation

One MSCA agreed to the proposed classification in general and another MSCA specifically agreed that an inhibition of brain or erythrocyte of more than 20 % is deemed relevant enough for classification purposes and agreed with classification with STOT RE 1. With reference to a previous RAC opinion on phosmet, also an inducer of acetylcholinesterase inhibition, IND proposed classification with STOT SE 1 because the cholinesterase activity is rarely associated with any clinical effect and inhibition is observed both after single and repeated exposure without evidence that the effect increases with increased duration of exposure. Therefore, it is unclear whether the observed inhibition is an acute or a repeated dose effect. In their response the DS pointed to the very much lower doses at which inhibition occurred following repeated dosing as compared to single dosing, and remained of the opinion that classification with STOT RE is justified.

Assessment and comparison with the classification criteria

An overview of the effects observed on cholinesterase inhibition and/or clinical signs in studies with repeated dosing of pyrimiphos-methyl is presented in Table S1 in the Background Document. This table includes some studies that were not mentioned in the CLH report but were present in the DAR.

It can be seen that the level of cholinesterase inhibition is dependent on dose but not so much on study duration. It was not always found to be (fully) reversible, with the activity of acetylcholinesterase in brain more slowly recovering than that in erythrocytes.

It can further be seen that in most studies clinical signs typical for organophosphates were not observed (nor were microscopical lesions in the nervous system), despite considerable inhibition of brain and erythrocyte acetylcholinesterase. In rats, clinical effects indicating neurotoxicity were not observed in any of the repeated dose studies described in the CLH report. RAC however notes that in these studies pirimiphos-methyl was tested at relatively low dose levels of 0.2-32 mg/kg bw/day, and that these levels hardly, if at all, induced general toxicity. Higher doses could therefore have been tested, which could possibly have resulted in clinical signs. This is supported by the findings at higher doses in a rat oral developmental toxicity study, which was not mentioned in the CLH report but was present in the DAR. In this (10-day) study, clear toxicity was observed at 150 mg/kg bw/day, but not at 1.5 and 15 mg/kg bw/day. The toxicity included clinical signs (abnormal gait, urinary incontinence, piloerection and body tremors), death (1/24 dams), and reduced maternal body weight gain (~ 50 %) and food consumption (~ 15 %). In mice, the doses tested were higher than in most rat studies, indeed resulting in general toxicity and signs of neurotoxicity. Severe toxicity at 178/284 mg/kg bw/day (m/f) (90-day study) and body weight loss at 72 mg/kg bw/day (chronic study) was evident within the first 1-2 weeks of treatment. Clinical signs indicating effects on the nervous system were observed from 36 mg/kg bw/day in the chronic study, and at 63/80 mg/kg bw/day (m/f) in the 90-day study. For dogs only a 2-year study was available, showing at the highest tested dose of 10 mg/kg bw/day loose faeces, vomiting and transient body weight effects. According to the study authors these effects may be secondary to the capsule dosing in a small volume (0.1 mL) to which the dogs adapted for the latter 80 % of the study. Given that the effects were already observed within the first weeks of the study, more severe effects might be expected in dogs in studies of shorter duration with higher dose levels.

RAC notes that in the available study summaries the time of onset of the clinical effects in rats, mice and dogs is not described. Hence, it is unclear whether the signs related to cholinergic inhibition appeared following repeated exposure or already in response to the first exposure(s). Comparison of the occurrence of clinical effects, after acute and repeated exposure, is only possible for rats (for mice and dogs there are no acute studies). Even for rats it can only be done on the basis of the developmental toxicity study, where gavage doses of 150 mg/kg bw/day resulted in abnormal gait, urinary incontinence, piloerection and body tremors, and one out of 24 dams dying. This observation contrasts with the absence of such effects in an acute oral neurotoxicity study with rats (also not mentioned in the CLH report but present in the DAR; see Table S2 under Supplemental information) at the same dose also by gavage. When further comparing the level of brain and erythrocyte acetylcholinesterase inhibition after acute and repeated exposure (see Table S3 under Supplemental information), it can be observed that comparable levels of inhibition after single exposure to 150 mg/kg bw/day can be achieved by much lower repeated exposures.

The above indicates that repeated exposure to a certain pirimiphos-methyl dose results in more severe effects than a single dose. Although there is limited evidence of accumulation of cholinesterase inhibition with repeated dosing, the slow recovery of brain and erythrocyte cholinesterase activity observed in some rat studies could be evidence of accumulation of the substance or its metabolites or slow reversibility of the binding to cholinesterase.

Based on the above comparisons (including the slow recovery of the inhibition), and assuming that also in mice and dogs the effects are not a response to the first exposure(s), RAC considers classification for STOT RE (as proposed by the DS) more appropriate than classification for STOT SE (as suggested during public consultation). Whereas there are indeed some similarities in the toxicity profile between the two acetylcholinesterase inhibitors, pirimiphos-methyl and phosmet, as remarked during public consultation, RAC notes also some differences. For phosmet, the level of acetylcholinesterase inhibition induced by a single dose of 22.5 mg/kg bw was at the same level (in erythrocyte) or higher (in brain) as that of a similar dose level in studies of longer

duration. For pirimiphos-methyl that was not the case (see comparison above). Moreover, in an acute neurotoxicity study, clinical signs typical for organophosphate exposure were observed at an oral phosmet dose of 36 mg/kg bw, i.e. a dose lower than those triggering the acute oral toxicity classification for phosmet (category 3, 50 < ATE ≤ 300 mg/kg bw). For pirimiphos-methyl, such clinical signs were observed in acute studies within the dose-range triggering its acute toxicity category 4 classification (300-2 000 mg/kg bw, ATE = 1 414 mg/kg bw).

According to the criteria, classification for STOT RE based on evidence from studies in animals requires significant and/or severe toxic effects of relevance to humans at low (category 1) or moderate (category 2) exposure. 'Significant' means changes which clearly indicate functional disturbance or morphological changes which are toxicologically relevant, whereas for 'severe' the effects are generally more profound or serious and significantly impact on health. Effects qualifying for classification include among others 'significant functional changes in the central or peripheral nervous systems or other organ systems, including signs of central nervous system depression and effects on special senses (e.g. sight, hearing and sense of smell)' (CLP Annex I 3.9.2.7.3(b)) and 'any consistent and significant adverse change in clinical biochemistry, haematology, or urinalysis parameters' (CLP Annex I 3.9.2.7.3(c)).

The DS considered a statistically significant and greater than 20 % inhibition of brain and erythrocyte acetylcholinesterase sufficient to fulfil the criteria, without the need to have adverse clinical effects indicative of neurotoxicity present. RAC notes that the cut-off of 20 % inhibition is used for risk assessment of acetylcholinesterase inhibitors, and that in general much higher reduction is needed for clinical effects to become manifest. From that perspective, placing the evidence/presence of clinical signs first in the hierarchy of adversity assessment of cholinesterase inhibition (conform the WHO JMPR guidance), might possibly meet the CLP requirement for adversity more than solely a ≥ 20 % inhibition of brain or erythrocyte acetylcholinesterase. Yet, also the inhibition seems to qualify, given criterion (c) above. Recognising the adversity, in particular of brain acetylcholinesterase inhibition, and that the degree of acetylcholinesterase inhibition that can be tolerated without clinical symptoms can vary between individuals and substances, RAC supports the approach of the DS. RAC subsequently supports the proposal for STOT RE 1; H372, because in most studies in rats, mice and dogs, a ≥ 20 % inhibition of brain or erythrocyte acetylcholinesterase was observed at dose levels around or below 10 mg/kg bw/day, the guidance value for STOT RE 1 for a 90-day oral study. RAC notes that the DS has extrapolated this guidance value for study durations other than 90 days, according to Haber's rule. It is however doubtful whether that is appropriate in this particular case, given that a maximum level of inhibition of erythrocyte acetylcholinesterase was already achieved after a couple of weeks of treatment, which did not further increase with longer study duration/treatment.

In the 3-week dermal toxicity study in rabbits, inhibition of erythrocyte cholinesterase activity was observed at all dose levels (4-400 mg/kg bw/day, on 5 days/week), some of which (or all, depending on whether extrapolation is appropriate) would warrant classification for STOT RE 1/2 (guidance values are 20 and 200 mg/kg bw/day, respectively, for a 90-day dermal study).

No repeated dose inhalation study was available. In an acute inhalation study (not mentioned in the CLH report but present in the DAR), inhibition of plasma and erythrocyte cholinesterase activity was observed, showing systemic bioavailability following inhalation exposure. Therefore, classification for STOT RE via the inhalation route cannot be excluded.

Overall, RAC supports classification of pirimiphos-methyl with **STOT RE 1; H372**, without specification of the route and with the **nervous system** as target organ.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

Pirimiphos-methyl was tested in a number of *in vitro* and *in vivo* studies for genotoxicity. For studies compliant with (or closely resembling) OECD test guidelines and GLP, the DS reported negative results for six *in vitro* studies and three *in vivo* studies in the CLH report. The *in vitro* studies concern two gene mutation tests in bacterial cells (Callendar, 1984; Sokolowski, 2015), one gene mutation test in L5178Y/TK± mouse lymphoma cells (Cross, 1986), two chromosome aberration tests in human lymphocytes (Wildgoose, 1986; Sokolowski, 2015a) and one SCE-test in Chinese hamster lung fibroblasts (Howard, 1986). *In vivo*, pirimiphos-methyl was tested in an UDS-assay in rats (Anon., 1998a) and in a micronucleus test (Rajini *et al*., 1986) and a dominant lethal test in mice (Anon., 1975a).

The DS further referred to four *in vitro* bacterial reverse mutation assays reported in public literature (Seiller, 1972; Seiller, 1976; Shirasu, 1984 and Hanna & Dyer, 1975). Several positive results were described for these studies that were conducted in the period 1972-1984. As they were not performed according to current standards and had limitations in the reporting, the DS considered them of low relevance.

With all guideline *in vitro* studies providing a clear unambiguous negative result, and noting further that the *in vivo* studies conducted did not provide evidence for a mutagenic effect, the DS argued that pirimiphos-methyl should not be classified for germ cell mutagenicity.

Comments received during public consultation

One MSCA supported the proposed classification in general. A second MSCA pointed to some discrepancies between the evaluation of studies in the DAR and in the CLH report. They indicated that the DAR presents a 5th *in vitro* bacterial mutation genotoxicity study reported in public literature (Moriya, 1983), also with positive results. They further noticed that the conclusion on the SCE assay (Howard, 1986) was equivocal in the DAR but negative in the CLH dossier. IND pointed to the existence of two new mutagenicity studies with pirimiphos-methyl (an *in vitro* HPRT test and an *in vivo* micronucleus test), both of which negative in their view. These studies were conducted for the renewal process, but were not available to the DS when drafting the CLH report. Full study reports of these two new studies have been provided to RAC, and they are summarised under Additional key elements (see Background Document).

Assessment and comparison with the classification criteria

In vitro

Two negative reverse gene mutagenicity tests in bacteria were available that were performed according to validated test guidelines. For the reasons specified by the DS, RAC agrees that the (partly positive) results of the four (or five; although according to the DAR the results of the Moriya study appear to have been presented in the Shirasu paper) additional bacterial tests from public literature are given little weight. Overall, pirimiphos-methyl is considered negative for reverse gene mutagenicity in bacteria.

RAC considers the SCE test (whether equivocal or negative) of low relevance, as it is no longer a standard test for regulatory purposes and more relevant *in vitro* tests on chromosome aberration in mammalian cells are available that showed pirimiphos-methyl to be negative for this effect.

RAC however considers pirimiphos-methyl to be positive for the induction of gene mutations in mammalian cells *in vitro*, based on the result obtained in the new HPRT study in the presence of metabolic activation. More weight is attached to this study than to the earlier negative L5178Y/TK± study, as that study deviated from the current OECD TG in expression period (72 hours is below the minimal required expression period of 7 to 9 days) and exposure duration (2 hours is below the suitable period of time of 3 to 6 hours).

In vivo

Regarding somatic cells, pirimiphos-methyl did not induce unscheduled DNA synthesis in rat liver cells or an increase in mouse bone marrow erythrocytes with micronuclei. Regarding germ cells, pirimiphos-methyl did not induce mutagenic effects in a mouse dominant lethal test.

Overall, the available data on pirimiphos-methyl do not meet the criteria and RAC agrees with the DS that **no classification for germ cell mutagenicity is warranted**.

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter's proposal

Two studies are available to inform on the carcinogenic potential of pirimiphos-methyl, a 2-year study in rats and a 78-week study in mice. The summaries below only relate to the neoplastic findings in these studies; the non-neoplastic findings have been summarized in the section on STOT RE. It is to be noted that as part of the pesticide renewal process, some new historical control data (HCD) were provided by the applicant to aid in the interpretation of the rat study.

Mice

In a GLP and OECD TG 451 compliant study (Anon. *et al.*, 1996), exposure of CD1-mice (50/sex/group) to 0, 50, 200 or 300 ppm pirimiphos-methyl in the diet (equivalent to 0, 9, 36 and 57 mg/kg bw/day) for 78 weeks did not result in treatment-related increases in incidences of neoplastic lesions. Pirimiphos-methyl was therefore concluded to be not carcinogenic in mice.

Rats

In a study pre-dating OECD TG and GLP, groups of 48 Wistar-derived rats/sex were fed diets containing 0, 10, 50 or 300 ppm pirimiphos-methyl (corresponding to mean intakes of 0, 0.4, 2.1 and 12.6 mg/kg bw/d) for 104 weeks (Anon., 1974). At the end of this period 8 rats/sex/dose were maintained on control diet for 4-8 weeks to assess recovery. Towards the end of the study, animals became ill with a respiratory infection and some died. All surviving animals were treated with oxytetracycline during week 86.

The DS noted that the level of detail in reporting was not to current standards, that no statistical analysis was conducted and that there are some inconsistencies within the report, but the overall level of information and investigation was concluded to be adequate.

Aside from some death due to respiratory infection (at its peak, 7, 3, 7 and 6 animals from the control, low, mid and high dose group, respectively, in one week), survival was not affected.

Marginally increased incidences of pancreatic and brain tumours were observed (see Table 1 below). The increases were compared to two sets of HCD. The first set was provided in the original DAR and covers 6 studies of varying terminology between 1965 and 1973. The second

set was provided for the renewal process and covers 23 studies in the same strain of rat as in the main study, from the same laboratory, over a period of 20 years (1984-2004).

The DS remarked that uncertainty lies in why the numbers of animals investigated for carcinogenic findings is lower than the total number of animals in the study. It is possible that the lower numbers account for the animals that died due to a respiratory infection that occurred earlier in the study; however there is no information in the study report to support this. In the available study reports, tumour data specifically for the 40 male and 40 females sacrificed after 104 weeks was not available.

The DS further remarked that a direct comparison cannot be made between the HCD and the current study as there is no information to indicate whether the studies ended at 104 weeks or whether they had a recovery period as with the current study. Nevertheless, the extended HCD were still considered to provide useful information, e.g. the pattern of findings in the HCD presented did not seem to change over the 20 year period.

Table 1*. Increased tumour incidences in rats fed pirimiphos-methyl*

	Males						**Females**					
Dose (ppm)	0	10	50	300	HCR[#] (%)	HCD* (%) [$]	0	10	50	300	HCR[#] (%)	HCD* (%) [$]
Total number of animals	48	48	48	48			48	48	48	48		
Animals investigated	42	43	45	42			43	45	46	47		
PANCREAS												
Islet cell adenoma	0	0	0	4 (9.5 %)	0-6	0-9.6 [15/23]	1 (2.3 %)	0	0	0	0-4	0-3.8 [9/23]
Islet cell carcinoma	0	0	0	1 (2.4 %)	0-7	0-3.8[§] [5/23]	0	0	0	0	0-2	0-1.9[§] [1/23]
BRAIN												
Meningioma (B)	1 (2.4 %)	1 (2.3 %)	2 (4.4 %)	2 (4.8 %)	0-4	0-3.8 [8/23]	0	0	1 (2.2 %)	0	0	0-1.9 [6/23]
Ependymoma (B/M)	0	0	0	0	0-5	0-1.9 [2/23]	0	0	0	1 (2.1 %)	0	0-1.9 [1/23]
Ganglioneuroma (B)	0	0	0	0	0	0	0	0	0	1 (2.1 %)	0	0

B – benign; M - malignant
[#] HCR - Historic control range from 6 studies with varying terminology from 1965-1973
[*] HCD – Historical control data for Alpk:APfsd Wistar BABU rats from the applicant's laboratory over a 20 year period from 1984-2004
[§] reported as adenocarcinoma
[$] number of studies with tumour findings

Pancreatic tumours

Compared to concurrent controls, there was an increased incidence of pancreatic islet cell adenoma in top dose males (4/42, 9.5 %). In addition, one top dose male had multiple tumours, including a pancreatic islet cell carcinoma. Both findings were however within the HCD provided, showing that up to 5/52 (9.6 %) adenoma and up to 2/52 carcinoma (3.8 %) can occur spontaneously in a study. Given that there were no pre-neoplastic lesions that might suggest a progression to cancer and no other signs of toxicity to the tissues, and that there was no increase in pancreatic tumours in female rats and in mice treated with pirimiphos-methyl, the DS considered the findings in male rats a natural occurrence in aged rats, unrelated to treatment.

Brain tumours

Some minor increases in brain tumours were observed. In male rats, there was an increase in benign meningioma in the mid and high dose group, both presenting 2 animals with this tumour versus 1 animal each in the control and low dose group. Whilst on a percentage basis this finding was above the HCD, historical control incidences of 1 to 2 animals per study are not uncommon. The DS therefore considered it insufficient evidence of a carcinogenic response.

In female rats, 1 top dose animal (2.1 %) was found to have an ependymoma and another top dose animal (2.1 %) a benign ganglioneuroma, associated with the pituitary gland. No ependymoma or ganglioneuroma were observed in the other treatment or control groups. As to HCD, no ependymoma were observed in the old set, whereas in the new set there was 1/23 studies with 1/52 animals spontaneously developing this tumour type (1.9 %). Hence, the finding of a single untreated animal with an ependymoma was not considered treatment-related by the DS. Neither the old nor the new HCD showed any incidence of females presenting a ganglioneuroma in the brain. However, the DS noted that the new HCD did show a spontaneous occurrence of tumours with the same aetiology in untreated male rats (1/52 (1.9 %) in the adrenals and 1/104 (1.0 %) in the thyroid gland).

Conclusion

The DS concluded that the tumours observed in the pancreas and brains of rats occurred spontaneously and were not related to treatment with pirimiphos-methyl. There were no pre-neoplastic lesions or any other toxicological findings that indicated these tissues were a target organ and no mechanistic basis for tumour formation, raising into question the biological plausibility of the findings. Furthermore, pirimiphos-methyl was found to be non-genotoxic in a battery of *in vitro* and *in vivo* tests and in a robust carcinogenicity study in mice, using higher doses, no tumours were observed. On the basis of the available evidence, pirimiphos-methyl should therefore not be classified for carcinogenicity.

Comments received during public consultation

One MSCA and IND supported the proposal for no classification for carcinogenicity. A second MSCA suggested that the HCD studies in the period 1984-2004 were not compliant and that the pancreatic tumours and brain meningioma should be discussed in more detail considering the weight of evidence. A third MSCA suggested classification in category 2, based on less than 50 animals/sex having been tested, the limited relevance of the HCD values from the period 1984-2004, and the observation that pirimiphos-methyl is a molecule with neurological tropism, raising concern as to the different types of brain tumours found.

In response, the DS agreed that the HCD from 1984-2004 are not contemporary to the 2-year rat study from 1974. Due to the rare nature of some of the findings, however, the DS found these HCD to provide some reassurance that these types of tumours can occur spontaneously in rats. Although the DS acknowledged that the number of animals investigated leaves some uncertainties, this is not believed to lead to a significant problem in interpreting the results as the number of animals were comparable across all dose groups (including the controls). The DS further stood by their arguments and conclusion presented in the CLH report that the pancreas and brain tumours are not related to treatment with pirimiphos-methyl.

Assessment and comparison with the classification criteria

In view of the absence of treatment-related increases in neoplastic effects in the mouse 78-week carcinogenicity study, RAC considers there is no evidence for carcinogenicity of pirimiphos-methyl in mice.

In contrast to mice, marginally increased incidences of pancreatic and brain tumours were observed in a 2-year rat study. RAC notes this study has some limitations in its design (somewhat lower number of animals tested than currently required (but still > 40 per group available for investigation), dose selection, no statistics performed), in its conduct (occurrence of respiratory infections), and in reporting (limited details). Regarding dose selection, RAC notes this may not have been appropriate, given that the rather low top dose of 12.6 mg/kg bw/day (4.5× lower than in mouse 78-week study) was devoid of toxicity (e.g. no effect on mortality, clinical signs, body weight and food consumption), aside from acetylcholinesterase inhibition.

In male rats an increase in islet cell adenoma of the pancreas was observed at the highest dose (4/42, 9.5 %) whereas no such tumours were observed in the concurrent controls or the other exposure groups, nor in the exposed females. Additionally, there was 1 top dose male with an islet cell carcinoma, but this animal had multiple tumours and it was not clear whether this carcinoma was a primary tumour or not. On a percentage basis, the incidence of adenoma was above the highest incidence observed in male rats in the old set of HCD (6 %, in 6 studies over 10 years prior to the 2-year rat study with pirimiphos-methyl from 1974), and just below the highest incidence observed in the new set of HCD (5/52 or 9.6 %, in 23 studies over a 20-year period between 1984 and 2004). The single occurrence of a carcinoma was within the HCD of both periods. RAC considers the comparison with both sets of HCD of limited value, the old set because a part was outside the window of 5 years before/after the performance of the 1974 rat study and no details were available to narrow it down, the new set because these are even less contemporary to the study under consideration. Furthermore, it is unclear whether the HCD concerned 104-week studies, or included a recovery period. The HCD do however indicate that over the approximately 30 years studied there is a consistent low level of spontaneous pancreatic tumour findings, with no evidence of a shift over time. Whereas for the increase in islet cell adenoma a relation with pirimiphos-methyl treatment cannot be totally excluded due to the study limitations and limited value of the HCD, RAC concludes on the basis of a weight of evidence assessment that it does not warrant classification because:

- no such increase was observed in female rats;
- no such increase was observed in mice;
- no pre-neoplastic lesions of the pancreas were observed in the study, nor in any of the other repeated dose toxicity studies with rats;
- pirimiphos-methyl was found to be non-genotoxic *in vivo*;
- it concerns benign tumours, whereas no increase in malignant tumours was observed;
- pancreatic islet cell adenoma and carcinoma seem to occur with low frequency in untreated male rats.

In male rats also a small increase in benign brain meningioma was observed at the two highest dose groups (1 extra case as compared to the concurrent control and low dose groups). Female rats did not show an increase in meningioma (single occurrence at the mid dose), but in the high dose group there was a single female with an ependymoma of the brain and a single female with a ganglioneuroma. The latter tumour is not a primary tumour of the brain, but arises from the sympathetic ganglia of the autonomic nervous system. Ganglioneuromas are rare, benign tumours that may appear in organs such as thyroid gland, adrenals and pituitary. According to the DAR, the female with the ganglioneuroma was having a pituitary growth, and the ganglioneuroma was not seen in several brain sections but was stated to have been associated with the pituitary. It might therefore have been a pituitary tumour, a common finding in aged rats. The available HCD of two periods show that brain meningioma and ependymoma, but not ganglioneuroma, occur spontaneously at low incidence in rats. Ganglioneuroma do however occur at low incidence in other organ types. As noted for the pancreatic tumours, RAC considers the comparison with the HCD of limited value because they were not contemporary. Whilst noting the study limitations, RAC concludes on the basis of a weight of evidence assessment that the brain tumours do not warrant classification because:

- the increases were very small;
- each tumour type only occurred in one sex;
- no increases in brain tumours were observed in mice;
- no pre-neoplastic lesions of the brain were observed in the study, nor in any of the other repeated dose toxicity studies with rats, including a sub-chronic neurotoxicity study with a slightly higher top dose;
- pirimiphos-methyl was found to be non-genotoxic *in vivo*;
- meningioma and ependymoma seem to occur with low frequency in untreated rats;
- the ganglioneuroma may have been misdiagnosed.

Overall, RAC therefore concurs with the DS that on the basis of the available data in mice and rats, **classification of pirimiphos-methyl for carcinogenicity is not warranted**.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

The pirimiphos-methyl is an active substance used as an insecticide in the meaning of Regulation (EU) No 1107/2009. It has a current entry in Annex VI to the CLP regulation for classification as Aquatic Acute 1 and Aquatic Chronic 1. Based on the available data on aquatic toxicity and fate of pirimiphos-methyl the dossier submitter (DS) proposed to update the environmental classification to Aquatic Acute 1 (M=1 000) and Aquatic Chronic 1 (M=1 000) according to CLP Regulation.

Degradability

A hydrolysis study according to U.S. EPA, Subdivision N, Section 161-1 and EEC Method C.7 guidelines, in compliance with GLP, was run at pH 4, 5, 7 and 9 at 25 °C for 30 days in the dark. Pirimiphos-methyl undergoes hydrolytic degradation, depending on the pH value, with the shortest DT_{50} values at acidic pH. The first order DT_{50} values at 25 °C were determined to be 2, 7, 117 and 75 days at pH 4, 5, 7 and 9 respectively. In neutral and basic conditions two degradation products R402186 and R046382 were formed whilst in acidic conditions only R046382 was observed.

The photodegradation of radio-labelled pirimiphos-methyl was studied according to EPA FIFRA 161-2 and 161-3 guidelines and in compliance with GLP. Pirimiphos-methyl degraded extensively with an estimated first order DT_{50} of 0.46 and 0.47 hours of Florida Summer Sunlight at pH 5 and 7 respectively. Photolysis of pirimiphos-methyl resulted in one major degradate R046382, reaching maximum 63 % AR at the end of the study at both pH values. A further degradate R290438 was formed up to 14.5 % during the study, but degraded rapidly to final levels of 2.8 % and 3.3 % AR at pH 5 and 7 respectively.

No studies on ready biodegradability are available.

A water/sediment simulation study, carried out according to BBA Guidelines Part IV, Section 5-1, 1990 and in compliance with GLP, was run using two different systems in dark conditions at 20°C ± 2 °C for up to 100 days. Under aerobic conditions pirimiphos-methyl dissipated relatively rapidly from the water phase in both test systems ($DissT_{50}$ less than 1day), partitioning to sediment was rapid. A primary degradation of pirimiphos-methyl in the whole water/sediment systems was also fairly rapid (10.3 days and 8.51 days). Pirimiphos-methyl was degraded by hydrolysis to form a major metabolite (R46382) up to approximately 60 % AR. A further

metabolite (R402186) reached a maximum of approximately 20 % AR after 30 days and declined to 2-4 % after 100 days. Volatilisation from water reached a maximum of 31.2 % AR. The total amount of volatiles reached a maximum of 35 % throughout the duration of the study.

Based on the information above, the DS concludes that pirimiphos-methyl is not considered to be rapidly degradable for the purposes of environmental classification according to guidance on Regulation (EC) 1272/2008.

Bioaccumulation

The Partition coefficient n-octanol/water of pirimiphos-methyl was > 4 at 20 °C (Husband, 1997).

An experimental aquatic BCF was available following GLP and OECD TG 305. The study used a mixture of radiolabelled and unlabelled test substance in a ratio of 1:1. A flow-through system was used with Killifish (*Oryzias latipes*) and two exposure concentrations: 10 and 1 µg/L. The exposure period ran for 28 days followed by a 14 day depuration period. The steady-state bioconcentration factor in whole fish, adjusted in 5 % lipid content, was 1 013.4.

Based on a BCF greater than 500 and a Log K_{ow} greater then 4, pirimiphos-methyl is considered to have a potential for bioaccumulation.

Ecotoxicity

The ecotoxicological test results from available acute and chronic toxicity studies in the CLH report performed on pirimiphos-methyl are summarized in the following table:

Method	**Test organism**	**Test system**	**Results**			**Test conc.**	**Reference**
			Endpoint	**LC_{50}/EC_{50} [mg/L]**	**NOEC [mg/L]**		
Fish							
Non-guideline Predates GLP	*Oncorhynchus mykiss*	Static 96 h	Mortality	0.404		nom	Anon. (1978)
Non-guideline Predates GLP	*Oncorhynchus mykiss*	Static 96 h	Mortality	0.200		nom	Anon. (1973a)
Non-guideline Predates GLP	*Cyprinus carpio*	Static 48 h	Mortality	1.400		nom	Anon. (1973a)
OECD TG 203 (1992) GLP	*Cyprinus carpio*	Flow-through 96 h	Immobility	0.76		mm	Anon. (2005)
OECD TG 204 (1992) GLP	*Oncorhynchus mykiss*	Flow-through 28 d	Growth	0.61	< 0.023	mm	Anon. *et al*. (1990)
Aquatic invertebrates							
EPA – 660/3-75-009 Predates GLP	***Daphnia magna***	**Static 48 h**	**Immobility**	**0.00021**		**nom**	Evered and Doma (1976)
OECD TG 202 (2004) GLP	*Daphnia magna*	Static 48 h	Immobility	0.000314		mm	Liedtke (2015)
OECD TG 202 (1984) GLP	***Daphnia magna***	**Static 21 d**	**Survival, growth, reproduction**		**0.000050**	**nom**	Rapley and Hamer (1991)

Algae							
OECD TG 201 GLP	*Pseudokirchneriella subcapitata*	Static 96 h	Growth rate and morphology	4.9	0.56	mm	Smyth *et al*. (1989)

Acute toxicity

Four acute studies to fish for the pirimiphos-methyl are reported by the DS. Only one of them (*Anon. 2005*) was performed according to OECD TG 203 and to GLP, for the others no guidelines were followed and the studies summary were not available. All of the provided LC_{50} values ranged from 1.4 to 0.2 mg/L.

For aquatic invertebrates two acute toxicity studies are available and included in the CLH Report; *Liedtke 2015*, performed according to OECD TG 202 (2004) and GLP criteria and *Evered and Doma 1976*, conducted following EPA-660/3-75-009 and pre-dated GLP certification.

In the relevant study by *Liedtke 2015*, the acute toxicity of pirimiphos-methyl *to Daphnia magna* was determined in a 48 h static test system following OECD TG 202 (GLP). Based on mean measured concentrations, the 48 h EC_{50} to *Daphnia magna* was 0.000314 mg/L. This study is considered acceptable with fulfilled validity criteria.

The lowest acute endpoint value was obtained in the acute toxicity study by *Evered and Doma 1976,* with a nominal 48 h EC_{50} of 0.00021 mg/L for *Daphnia magna*. However the study cannot be regarded as valid because measured concentrations are available only for two test concentration, showing that the range of 80-120 % of the nominal is not achieved. Therefore, no measured concentrations are available and nominal concentrations are inadequate for deriving the acute end-point.

Therefore, the mean measured 48 h EC_{50} of 0.000314 mg/L is regarded as the most sensitive endpoint used for aquatic acute classification.

A single algal study (*Smith et al. 1989*) for pirimiphos-methyl is provided in the CLH Report. This study is a 96 h static test, performed according to OECD TG 201 and GLP compliant, and provides both acute and long-term endpoints. Based upon mean measured concentrations, a 96 h E_rC_{50} value of 4.9 mg/L and a NOE_rC of 0.56 mg/L have been determined for the effects of pirimiphos-methyl on growth rate of green algae *Pseudokirchneriella subcapitata*.

Chronic toxicity

A single chronic toxicity study to fish is available (*Anon. et al., 1990*). The study was a prolonged toxicity test to *Oncorhynchus mykiss* based on OECD TG 204 guideline and GLP compliant. A 28 day NOEC value of < 0.023 mg/L was determined based on mean measured concentrations. Although the study is considered valid, is not considered suitable as a long term study, being a prolonged acute study with fish mortality as the major endpoint examined.

A single chronic toxicity study on aquatic invertebrates (*Rapley and Hamer, 1991*) is provided as valid key study in the CLH Report. The chronic toxicity of pirimiphos-methyl to *Daphnia magna* was determined in a 21-day static test system, according to OECD TG 202 (1984) and GLP criteria. The mean measured concentrations were within 80-120 % of the nominals. The overall 21 day nominal NOEC for all tested endpoints (survival, growth, reproduction) was 0.000050 mg/L for *Daphnia magna*. This is regarded as the most sensitive endpoint used for aquatic chronic classification.

Comments received during public consultation

Four Member States (MS) and two organisations (ORG) contributed during public consultation stating a general agreement with the proposed environmental classification. Two MS noted some editorial errors, which were clarified by the DS.

Assessment and comparison with the classification criteria

Degradability

RAC agrees with the DS proposal to consider pirimiphos-methyl as not rapidly degradable. The degradation information does not provide sufficient data to show pirimiphos-methyl is ultimately degraded with a half-life < 16 days (equivalent to a degradation > 70 % within 28 days), or transformed to non-hazardous products as there is no available ecotoxicity data on the degradation products.

Bioaccumulation

The experimental whole fish BCF value for pirimiphos-methyl is 1 013.4, greater than the CLP trigger values of 500. The test is valid and usable for the purposes of classification.

The log K_{OW} value of 4.2 is above the CLP trigger value of 4 intended to identify substances with a potential to bioaccumulate.

In conclusion, RAC agrees with the DS that pirimiphos-methyl is considered to have a potential to bioaccumulate under CLP.

Aquatic toxicity

Acute aquatic hazard

Aquatic invertebrates are the most sensitive species, the lowest valid acute end-point is a 48 h EC_{50} of 0.000314 mg/L based on mean measured concentrations. This value is below the classification criterion of ≤ 1 mg/L for the hazard category Aquatic Acute 1. The appropriate M-factor is 1 000, since the toxicity is within the range ($0.0001 < L(E)C_{50} \leq 0.001$).

Chronic aquatic hazard

The most sensitive organisms are aquatic invertebrates with a 21 d NOEC = 0.000050 mg/L based on nominal concentrations. The study is reliable and usable for the classification purposes. This value is lower than the classification criterion for aquatic Chronic Category 1 (0.1 mg/L) for not rapidly degradable substances in the aquatic environment. The appropriate M-factor is 1 000, since the toxicity is within the range of $0.00001 < EC_{10}$ (NOEC) ≤ 0.0001. However, as there aren't valid long-term toxicity data for fish the lowest acute toxicity value must be compared with the CLP criteria following table 4.1.0(b)(iii). The highest reliable acute toxicity for fish is a value of 0.76 mg/L, which results in a classification of aquatic Chronic 1 with an M-factor of 1 for a not rapidly degradable substance ($0.1 < L(E)C_{50} \leq 1$). As the most stringent outcome is used for classification, pirimiphos-methyl should be classified as Aquatic Chronic 1, M-factor = 1 000.

In summary, RAC agrees with the DS that Pirimiphos-methyl should be classified as:

Aquatic Acute 1; H400, M-factor of 1 000;

Aquatic Chronic 1; H410, M-factor of 1 000.

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).