Conclusion regarding the peer review of the pesticide risk assessment of the active substance

pirimiphos-methyl

finalised: 10 August 2005

SUMMARY

Pirimiphos-methyl is one of the 52 substances of the second stage of the review programme covered by Commission Regulation (EC) No 451/2000[1], as amended by Commission Regulation (EC) No 1490/2002[2]. This Regulation requires the European Food Safety Authority (EFSA) to organise a peer review of the initial evaluation, i.e. the draft assessment report (DAR), provided by the designated rapporteur Member State and to provide within one year a conclusion on the risk assessment to the EU-Commission.

United Kingdom being the designated rapporteur Member State submitted the DAR on pirimiphos-methyl in accordance with the provisions of Article 8(1) of the amended Regulation (EC) No 451/2000, which was received by the EFSA on 4 November 2003. Following a quality check on the DAR, the peer review was initiated on 4 December 2003 by dispatching the DAR for consultation of the Member States and the sole notifier Syngenta. Subsequently, the comments received on the DAR were examined by the rapporteur Member State and the need for additional data was agreed in an evaluation meeting on 25 May 2004. Remaining issues as well as further data made available by the notifier upon request were evaluated in a series of scientific meetings with Member State experts in September and October 2004.

A final discussion of the outcome of the consultation of experts took place with representatives from the Member States on 19 July 2005 leading to the conclusions as laid down in this report.

The conclusion was reached on the basis of the evaluation of the representative uses as insecticide as proposed by the notifier which comprises spraying to wheat, barley and oats grains during storage and treatment for structural surfaces in empty grain stores at an application rate up to of 4 g pirimiphos-methyl per tonne and 50 g per 100 m², respectively. Pirimiphos-methyl can be used as insecticide and acaricide.
The representative formulated product for the evaluation was "Actellic 50EC", an emulsifiable concentrate (EC), registered in several countries in Europe.

[1] OJ No L 53, 29.02.2000, p. 25
[2] OJ No L 224, 21.08.2002, p. 25

Adequate methods are available to monitor all compounds given in the respective residue definition. Residues in food of plant and animal origin can be determined with a multi-method. For the other matrices only single methods are available to determine residues of pirimiphos-methyl.
Sufficient analytical method as well as methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection product are possible.

Pirimiphos-methyl is extensively metabolised in rats. The acute oral toxicity is moderate and it is of low inhalatory and dermal toxicity. Pirimiphos-methyl was slightly irritating to skin and eye as well as induced mild sensitization. Classification for acute toxicity is needed and the proposed risk phrase is: Xn; R22 "Harmful if swallowed". Main effect is inhibition of acetyl cholinesterase activity. Pirimiphos-methyl was not genotoxic. No carcinogenic potential was evident in the mouse. Some rare brain and pancreatic tumours were seen in the rat study of old date and as a precautionary approach the classification and risk phrase is proposed Xn; R40 "Limited evidence of a carcinogenic effect".
No effect on reproductive performance was observed. Evidence of foetotoxicity, shifted pelvic position, was present at a high dose level. The effect is rather uncommon and the experts concluded that this finding was a variation and not a malformation and classification with R63 was not proposed.
The acceptable daily intake (ADI) is 0.004 mg/kg bw/day based on the 2-year studies from rat and dog with an overall safety factor of 100 (supported by human data) applied. The acceptable operator exposure level (AOEL) is 0.02 mg/kg bw/day based on the 2-year dog study (time point 13 weeks) and the 13-week neurotoxicity study in the rat with the safety factor of 100 applied, supported by human data. The acute reference dose (ARfD) is 0.15 mg/kg bw.
The representative formulation Actellic 50EC is used as admixture and for structural treatment. The estimated exposure for admixture, large scale automated treatment, is below the AOEL. However, **based on available data for structural treatment the estimated operator exposure is above the AOEL**

The decline of pirimiphos-methyl and the pattern of degradation products were similar in stored grain and after processing, even though the rate of decline strongly depended on the moisture content of the grain. Unchanged pirimiphos-methyl was the major residue found in grain and processed cereal products. Main metabolites were hydroxypyrimidine compounds, whereof 90% accounted for R046382[3]. The only metabolite considered to be of toxicological significance was R036341[4]. This metabolite was looked for in residue trials and processing studies and was shown to not form a significant part of the residue given the high levels of pirimiphos-methyl.
Pirimiphos-methyl is classified as fat soluble. However, if grain treated according to the cGAP is fed to livestock animals no residues above the limit of quantification (LOQ) are expected to occur in food of animal origin.
Chronic consumer exposure from the use of pirimiphos-methyl as a structural treatment to empty stores is of no concern. **With regard to chronic consumer exposure from the grain admixture**

[3] R046382: 2-diethylamino-4-hydroxy-6-methylpyrimidine
[4] R036341: *O*-2-ethylamino-6-methylpyrimidin-4-yl *O,O*-dimethylphosphorothioate

use, the ADI is exceeded for all considered consumer subgroups. An acute dietary risk for consumers exposed to pirimiphos-methyl residues on wheat, barley and oat grain is not expected from both uses evaluated.

Use of pirimiphos methyl will be restricted to indoor use for storage facilities treatment and stored cereals after harvest. Concentrations of pirimiphos-methyl in the air compartment are expected to be negligible, due to low volatility and short persistence in the atmosphere. Contamination of natural environments (soils and surface waters) through volatilization and deposition may be precluded.
Studies to investigate the fate of pirimiphos methyl in the different environmental compartments are not required. However, aqueous hydrolysis and photolysis was investigated and results are summarized in the physical and chemical properties and fate and behaviour sections of the DAR. No readily biodegradability test is available, the substance may be considered as not readily biodegradable. Whereas, data available indicate that pirimiphos-methyl may be significantly volatilised from soil and leaf surfaces, concentrations of pirimiphos-methyl in the air compartment are expected to be negligible due to short persistence in the atmosphere. Contamination of natural environments through volatilization and deposition should be avoided with adequate measures to minimize the emissions from the storage facilities.

The risk to birds, wild mammals, aquatic organisms, bees and non-target arthropods, soil micro- and micro organisms, including earthworms, non-target plants and biological methods for sewage treatment is considered low based on the use pattern of pirimiphos-methyl which is limited to enclosed food storage areas.

Key words: pirimiphos-methyl, peer review, risk assessment, pesticide, acaricide, insecticide

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BACKGROUND

Commission Regulation (EC) No 451/2000 laying down the detailed rules for the implementation of the second and third stages of the work program referred to in Article 8(2) of Council Directive 91/414/EEC, as amended by Commission Regulation (EC) No 1490/2002, regulates for the European Food Safety Authority (EFSA) the procedure of evaluation of the draft assessment reports provided by the designated rapporteur Member State. Pirimiphos-methyl is one of the 52 substances of the second stage covered by the amended Regulation (EC) No 451/2000 designating United Kingdom as rapporteur Member State.

In accordance with the provisions of Article 8(1) of the amended Regulation (EC) No 451/2000, United Kingdom submitted the report of its initial evaluation of the dossier on pirimiphos-methyl, hereafter referred to as the draft assessment report, to the EFSA on 4 November 2003. Following an administrative evaluation, the EFSA communicated to the rapporteur Member State some comments regarding the format and/or recommendations for editorial revisions and the rapporteur Member State submitted a revised version of the draft assessment report. In accordance with Article 8(5) of the amended Regulation (EC) No 451/2000 the revised version of the draft assessment report was distributed for consultation on 4 December 2003 to the Member States and the main notifier Syngenta as identified by the rapporteur Member State.

The comments received on the draft assessment report were evaluated and addressed by the rapporteur Member State. Based on this evaluation, representatives from Member States identified and agreed in an evaluation meeting on 25 May 2004 on data requirements to be addressed by the notifier as well as issues for further detailed discussion at expert level.

Taking into account the information received from the notifier addressing the request for further data, a scientific discussion of the identified data requirements and/or issues took place in experts' meetings organised on behalf of the EFSA by the Pesticides Safety Directorate in York, United Kingdom in September and October 2004. The reports of these meetings have been made available to the Member States electronically.

A final discussion of the outcome of the consultation of experts took place with representatives from Member States on 19 July 2005 leading to the conclusions as laid down in this report.

During the peer review of the draft assessment report and the consultation of technical experts no critical issues were identified for consultation of the Scientific Panel on Plant Health, Plant Protection Products and their Residues (PPR).

In accordance with Article 8(7) of the amended Regulation (EC) No 451/2000, this conclusion summarises the results of the peer review on the active substance and the representative formulation

evaluated as finalised at the end of the examination period provided for by the same Article. A list of the relevant end points for the active substance as well as the formulation is provided in appendix 1.

The documentation developed during the peer review was compiled as a **peer review report** comprising of the documents summarising and addressing the comments received on the initial evaluation provided in the rapporteur Member State's draft assessment report:

- the comments received
- the resulting reporting table (rev. 1.2 of 1 July 2004)
- the consultation report

as well as the documents summarising the follow-up of the issues identified as finalised at the end of the commenting period:

- the reports of the scientific expert consultation
- the evaluation table (rev. 1-2 of 9 August 2005)

Given the importance of the draft assessment report including its addendum (compiled version of July 2005 containing all individually submitted addenda) and the peer review report with respect to the examination of the active substance, both documents are considered respectively as background documents A and B to this conclusion.

THE ACTIVE SUBSTANCE AND THE FORMULATED PRODUCT

Pirimiphos-methyl is the ISO common name for *O*-2-diethylamino-6-methylpyrimidin-4-yl *O*,*O*-dimethylphosphorothioate (IUPAC).

Pirimiphos-methyl belongs to the class of organothiophosates insecticides/acaricides such as diazinon and azinphos-methyl or dimethoate, respectively. Pirimiphos-methyl inhibits the acetyl cholinesterase activity.

The representative formulated product for the evaluation was "Actellic 50EC", an emulsifiable concentrate (EC), registered in several countries in Europe.

The evaluated representative uses as insecticide comprise spraying to control a broad spectrum of insects in wheat, barley and oats grains during storage and treatment for structural surfaces in empty grain stores at an application rate up to of 4 g pirimiphos-methyl per tonne and 50 g per 100 m², respectively. Pirimiphos-methyl can be used as insecticide and acaricide.

SPECIFIC CONCLUSIONS OF THE EVALUATION

1. Identity, physical/chemical/technical properties and methods of analysis

The minimum purity of pirimiphos-methyl as manufactured should not be less than 880 g/kg, which is higher than the minimum purity given in the FAO specification 239/a/TC/S (1988) of 860 g/kg. The higher value relates to the submitted results of current batch analysis and not to any toxicological concern to increase the minimum purity.
The technical material contains no relevant impurities.

The content of pirimiphos-methyl in the representative formulation is 500 g/L (pure).

The assessment of the data package revealed no particular area of concern.
The main data regarding the identity of Pirimiphos-methyl and its physical and chemical properties are given in appendix 1.

Sufficient test methods and data relating to physical, chemical and technical properties are available. Also adequate analytical methods are available for the determination of pirimiphos-methyl in the technical material and in the representative formulation.
Therefore, enough data are available to ensure that quality control measurements of the plant protection product are possible.

Adequate methods are available to monitor all compounds given in the respective residue definition, i.e. pirimiphos-methyl in food of plant and animal origin and air. For the compartments soil and water no residue definition is proposed. However, sufficient analytical methods are available for the determination of pirimiphos-methyl to cover emergency measures in the case of an accident.
Residues in food of plant and animal origin can be determined with a multi-method (the German S19 method has been validated). For the other matrices only single methods are available to determine residues of pirimiphos-methyl.
The methodology used is GC with MS or PN detection.

The discussion in the experts' meeting on identity, physical and chemical properties and analytical methods was limited to missing ILV for food of animal origin and some clarification regarding residue analytical methods. These clarifications are given at the moment only in the "evaluation table" (rev. 0-2).

2. Mammalian toxicology

Pirimiphos-methyl was discussed at EPCO experts' meeting for mammalian toxicology (EPCO 14) in October 2004.

2.1 ABSORPTION, DISTRIBUTION, EXCRETION AND METABOLISM (TOXICOKINETICS)

Pirimiphos-methyl is rapidly and nearly completely absorbed (> 80%). Approximately 70% is excreted via urine and 10% via biliary excretion after 12 hours (conclusion of the experts' meeting).
Since there were discrepancies in the DAR regarding the presented ADME studies, especially the biliary proportion, there was a need to discuss the oral absorption at an experts' meeting. The meeting agreed (except one MS) that there were sufficient evidence to support an oral absorption of > 80%.
There are no data on the distribution pattern of pirimiphos-methyl. The degree of accumulation seems to be low (less than 2% remained in the carcass and tissues). However, females had a high concentration (200 times) in abdominal fat when exposed to 250 mg/kg bw as compared to the 1 mg/kg bw group. Pirimiphos-methyl is extensively metabolised and the major metabolites, which are also found in the goat and cow, are R035510[5], R046382[6] and desethyl-R402186[7].

2.2 ACUTE TOXICITY

The acute oral toxicity is moderate i.e. LD_{50} 1414 mg/kg bw and of low inhalatory and dermal toxicity, LC_{50} > 4.7 mg/L air (4 hours, nose only) and LD_{50} > 2000 mg/kg bw, respectively. Pirimiphos-methyl was slightly irritating to skin and eye as well as induced mild sensitization in 2 out of 20 guinea pigs at 25% and 50% challenge (Magnusson and Kligman test), but not classifiable. **Classification for acute toxicity is needed and the proposed risk phrase is: Xn; R22 "Harmful if swallowed".**

2.3 SHORT TERM TOXICITY

The short term effects of pirimiphos-methyl were studied in one 28-day and one 90-day study in the rat and one 90-day study in the mouse as well as a 2- year dog study. The dermal toxicity was studied in a 21-day study in the rabbit which however was not considered to be of acceptable quality. No repeat inhalation study is submitted.
Generally in all species, the main effect is inhibition of acetyl cholinesterase activity. Some of the results regarding erythrocyte effect were somewhat inconsistent and thus effects on brain acetyl cholinesterase activity were the primary determinant of adversity in lack of clinical signs.
Relevant NOAELs; 0.5 and 2 mg/kg bw/day, from the 2-year dog study, at the 12-month or 12-week time point, respectively.

2.4 GENOTOXICITY

In the DAR the genotoxic properties of pirimiphos-methyl were studied in a battery consisting of five *in vitro* studies (Ames test, gene mutation, clastogenicity and sister chromatid exchange). Two *in vivo* studies were submitted, UDS test and dominant lethal study in the mouse. In addition, a number of studies from the open literature are summarised in the DAR. The purity is in most cases lower than the minimum purity specified.

[5] R035510: 2-ethylamino-6-methyl-pyrimidin-4-ol
[6] R046382: 2-diethylamino-4-hydroxy-6-methylpyrimidine
[7] desethyl-R402186: *O*-2-ethylamino-6-methylpyrimidin-4-yl *O*-methyl phosphorothioate

Contradictory results were obtained in bacterial mutation tests. A mutagenic potential was reported in several studies in the open literature. However, in the study submitted by the notifier a negative result was obtained. It was neither mutagenic nor clastogenic. A small increase in sister chromatid exchanges was found, however in the absence of dose response relationship the biological relevance was questioned. The results in the *in vivo* studies were all negative. This issue was discussed at the experts´ meeting and the experts agreed that there were sufficient evidence to conclude that pirimiphos-methyl was not genotoxic *in vivo*.

2.5 LONG TERM TOXICITY

One long term toxicity study in the rat of old date, 1974, and one in the mouse from 1996 were submitted in the dossier and are presented in the DAR. The rat study was not performed according to GLP and the level of reporting was not up to current standards. The primary effect is inhibition of cholinesterase activity.

Some rare brain and pancreatic tumours were seen at 12.6 mg/kg bw/day (highest dose level). Although these were within the historical control range it is not possible to discount the assumption that pirimiphos-methyl might have carcinogenic potential at higher dose levels. Within the limitations of the study a NOAEL is considered to be 0.4 mg/kg bw/day based on brain acetyl cholinesterase effects at 2.1 mg/kg bw/day.

In the mouse study, no carcinogenic potential was evident. However, a NOAEL could not be identified since there were effects on erythrocyte and brain acetyl cholinesterase evident at all dose levels. The LOAEL is 9 mg/kg bw/day.

The relevance of the brain and pancreatic tumours were discussed at the experts´ meeting. Additional historical control data had been requested by the notifier but not submitted. In the absence of this data, the rapporteur Member State proposed R40 due to the uncertainties in the results from the old rat study and the equivocal relevance of the occurrence of tumours. The experts agreed with this precautionary approach. **Therefore, the risk phrase Xn; R40 is proposed "Limited evidence of a carcinogenic effect"** and the final decision is to be made by ECB.

2.6 REPRODUCTIVE TOXICITY

The reproductive effect of pirimiphos-methyl was studied in one 2-generation study in rats. There were no direct effects on reproductive performance or fertility observed. The parental NOAEL was 1 mg/kg bw/day based on marked body weight reduction and inhibition of acetyl cholinesterase activity. No effect on reproduction was observed and the relevant NOAEL for reproduction was >12 mg/kg bw/day.

In order to examine teratogenic or developmental effects of pirimiphos-methyl one study in the rabbit was submitted in the dossier and evaluated in the DAR. Evidence of foetotoxicity, such as shifted pelvic position, was present at a high dose level, 48 mg/kg bw/day. However signs of maternal toxicity were observed at this dose level (reduction in acetyl cholinesterase activity). The effect is rather uncommon and the rapporteur Member State concluded that this more reflect a foetotoxic effect than a teratogenic effect. This issue was discussed at the experts´ meeting and whether a

classification with R63 was appropriate. The meeting considered the findings as a boarderline effect and a variation and not a malformation. Classification with R63 was not supported.
The NOAEL for maternal effects is 12 mg/kg bw/day and the developmental NOAEL is > 48 mg/kg bw/day in the rabbit and > 150 mg/kg bw/day in the rat. The NOAEL for foetotoxicity was considered to be 24 mg/kg bw/day based on the observed pelvic shift.

2.7 NEUROTOXICITY

The studies on neurotoxicity are presented under further toxicological studies in the DAR (B.6.8). Acute as well as short term (13-week) neurotoxicological studies were performed in the rat. The primary effect is inhibition of cholinesterase activity in both brain and erythrocytes. The acute NOAEL is 15 mg/kg bw and the short term NOAEL is 2.1 mg/kg bw/day. No evidence of delayed neurotoxicity (NTE activity) was recorded in hens.

2.8 FURTHER STUDIES

Human volunteer study

Two studies on human volunteers are reported, one 28-day and one 56-day study, both performed in 1976. Pirimiphos-methyl was administered via gelatine capsules at a single dose level of 0.25 mg/kg bw/day.
In both studies effects on plasma and erythrocyte cholinesterase activity was measured. Generally, no effects were observed and the NOAEL is thus 0.25 mg/kg bw/day.
Initially, the rapporteur Member State proposed to use the NOAEL from the human studies for deriving the reference values ADI and AOEL. The scientific validity of the studies was discussed at the experts´ meeting. The studies followed the declaration of Helsinki, but were old, not according to GLP and measurements of brain cholinesterase could not be performed. It was also a concern that human studies rarely measure the full range of parameters as compared to animal studies. Although some major draw backs, the studies were considered as scientifically valid.

Studies on metabolites

No specific studies are available on R046382 which is a major metabolite in rat metabolism studies.

2.9 MEDICAL DATA

Reports of signs/symptoms in operators is rare (in UK) given the extent of use.

2.10 ACCEPTABLE DAILY INTAKE (ADI), ACCEPTABLE OPERATOR EXPOSURE LEVEL (AOEL) and ACUTE REFERENCE DOSE (ARfD)

ADI and AOEL

Initially, the rapporteur Member State proposed to use the NOAEL of 0.25 mg/kg bw/day from the human studies for deriving the reference values ADI and AOEL. By using the safety factor of 10 the rapporteur Member State proposed ADI and AOEL of 0.03 mg/kg bw/day.

The setting of ADI and AOEL, in relation to using NOAELs derived from human studies, was questioned by several Member States and the setting of the reference values was discussed at the experts' meeting. The scientific value of the human studies was agreed on although they were old and not according to GLP (see 2.8 above).

The meeting agreed to base the ADI on the NOAEL of 0.4 mg/kg bw/day from the 2-year rat study combined with the NOAEL of 0.5 mg/kg bw/day from the 2-yr dog study. Since the rat study was old and of poor quality it was discussed whether the safety factor should be increased to account for the uncertainties related to the poor quality of the study (see 2.5). However, on the contrary when considering the NOAEL of 0.25 mg/kg bw/day from the human studies, the applied safety factor would possibly be lower than 100. The exact figure was not agreed on, for consideration for setting the ADI exposure based on 28-days or 56-days exposure to humans does not mimic a life time exposure, also concerns regarding the absence of investigations of the full range of parameters.
Therefore, the experts agreed to set the ADI on the NOAEL of 0.4 mg/kg bw/day, supported by the NOAEL of 0.25 mg/kg bw/day from the human studies with an overall safety factor of 100. **The resulting ADI is 0.004 mg/kg bw/day** based on the 2-year studies from rat and dog with an overall safety factor of 100 (supported by human data) applied.

The setting of AOEL was discussed at the expert´ meeting. The experts agreed to base the AOEL on the NOAEL of 2 mg/kg bw/day from the 2-year dog (time point 12 weeks) and the 13-week neurotoxicity study in the rat supported by the human data. The degree of oral absorption was discussed at the experts´ meeting, and it was agreed that the oral absorption was > 80% (see 2.1). Thus, no oral correction for the AOEL is needed.
The resulting AOEL is 0.02 mg/kg bw/day based on the 2-yr dog study (time point 12 weeks) and the 13-week neurotoxicity study in the rat with the safety factor of 100 applied, supported by human data.

ARfD
The ARfD is based on the NOAEL of 15 mg/kg bw/day from the acute neurotoxicity study in the rat, with 100 as safety factor.
The ARfD is 0.15 mg/kg bw.

2.11 DERMAL ABSORPTION

In vitro studies on the rat and human skin were performed in order to set dermal absorption value for the formulation with the Actellic 50EC.
The dermal penetration in rat skin was high however the penetration rate through human skin was lower approximately 25 fold for concentrate or 11 fold for dilution based on total absorption after 24 hours. Taking this into consideration, the rapporteur Member State proposed a dermal absorption value of 1% for the concentrate and 10% for the dilution.

2.12 EXPOSURE TO OPERATORS, WORKERS AND BYSTANDERS

The representative plant protection product is Actellic 50EC which contains 500 g pirimiphos-methyl/L and is to be used as an admixture on stored grain and as a structural treatment for empty grain stores.

Operator exposure

The product can be applied either as a complete admixture with the entire bulk of stored grain or as a surface admixture with a treated layer 30 to 100 cm deep enclosing the bulk of untreated grain. In both situations, grain is normally treated using a static sprayer positioned above the conveyor belt as grain is loaded into the store. However, it is possible that small-scale users may apply Actellic 50EC using a knapsack sprayer. The product is also used as a structural treatment for empty grain stores, and is applied to all surfaces using a knapsack sprayer, hand lance, or mistblower. According to the intended uses submitted by the notifier the maximum applied dose is 4 g pirimiphos-methyl/t, for admixture and 50 g pirimiphos-methyl /100 m^2 for structural treatment.

EFSA note: In the conclusion report, the estimated operator exposure is recalculated in accordance to the revised AOEL of 0.02 mg/kg bw/day. No addendum has been produced by the rapporteur Member State and thus the calculations provided in the DAR are not correct, they are based on the AOEL of 0.03 mg/kg bw/day as proposed initially by the rapporteur Member State. However, a reasoned statement regarding the use structural treatment is provided in the addendum 2 (June, 2005).

1. Grain admixture

i) Large scale, automated hydraulic sprayer

Commercial stores

The estimates are based on the assumed work rate of 240 ton/8h. The notifier had provided an estimation of operator exposure based on mixing/loading data from the UK-POEM. The estimated total exposure was 0.00025-0.0025 mg/kg bw/day which according to the new AOEL of 0.02 mg/kg bw/day corresponds to 1-12.5% of AOEL, depending on level of worn PPE, see table below.

Farm users

The estimates are based on the assumed work rate of 130 ton/6h. The notifier had provided an estimation of operator exposure based on mixing/loading data from the UK-POEM. The estimated total exposure was 0.00016-0.0016 mg/kg bw/day which according to the new AOEL of 0.02 mg/kg bw/day corresponds to 0.8-8% of AOEL, depending on level of worn PPE, see table below.

ii) Small scale, handheld equipment, knapsack application

No estimate was provided.

2. Structural treatment

A) Estimations on operator exposure based on model calculations

The formulation is also used for treatment of empty grain stores using knapsack sprayer, hand lance or mist blower.

For farm users the calculated throughput was 2 hours/day and for large scale users (commercial) the calculated throughput was 6 hours/day.

According to calculations based on the UK Health and Safety Executive (HSE) exposure data from the similar application of *in situ* timber treatments assuming a 6 hour work day and body weight of 60 kg, the predicted total exposure was exceeding the AOEL to a great extent.

In the worst case scenario, with additional PPE as well as respiratory personal equipment (RPE) the AOEL was exceeded by more than 50 000% for the commercial use. The AOEL for farm use was also exceeded by more than 16 000% according to worst case scenario estimation. Corresponding estimates based on the median value also show that the AOEL is exceeded for both commercial and farm use, see table below. Since the AOEL was revised at the experts' meeting, from 0.03 to 0.02 mg/kg bw/day the estimated operator exposure has been recalculated.

Estimated exposure presented as % of AOEL (0.02 mg/kg bw/day) based on UK POEM and Health and Safety Executive data

Treatment		**With PPE (coverall)**	**With PPE + RPE**
Admixture*	i) Large scale, automated Commercial Farm	 1.25% 0.8%	
Structural§	i) Commercial ii) Farm	730 - 52 815% 245 - 17 605%	555 - 50 540% 185 - 16 845%

* based on UK-POEM M/L data. § based on UK HSE generic exposure data, median value to worst case, for remedial timber treatment in situ.

B) Estimations on operator exposure based on a field study (biomonitoring)

The notifier had conducted a field study in 2002 on 10 mixer and loader applicators (all professionals except one that was a farm owner) and it is presented in the DAR. The study was conducted in accordance with OECD guidelines and GLP. The workers wore impermeable coverall with impermeable hood, protective gloves, rubber boots, face protection (face shield) and respiratory equipment (at least FFP3).

The estimations were based on the assumption that the metabolites R035510 and R046382 recovered in urine can be used as a surrogate for pirimiphos-methyl, accounting for 30%. Adjustments for the relative weight of pirimiphos-methyl and respective metabolite were also performed. Creatinine was used as a marker. There was a considerable variation in the daily excretion of creatinine for 5 of the 10 participants.

The estimated absorbed dose ranged from 0.0007 to 0.0314 mg/kg bw/day. When comparing this systemic dose to the AOEL of 0.02 mg/kg bw/day the estimated exposure is from 4 – 157% of the AOEL and the mean would be 42%.
Since the AOEL was revised, at the experts´ meeting, from 0.03 to 0.02 mg/kg bw/day, new calculations are provided in the conclusion report.

The study has some major drawbacks for instance, the assumption that human toxicokinetics are totally similar to rat toxicokinetics. In addition, the assumption that the metabolites used as a surrogate of pirimiphos-methyl corresponds to 30% of pirimiphos-methyl. Furthermore, there were uncertainties related to the incomplete urine sampling. Thus, the quality of the study is poor.

However, the rapporteur Member State is of the opinion that the biomonitoring study estimates are appropriate and valid. Furthermore, the rapporteur Member State assumes that a single exceedence of the AOEL is not of a concern due to the rapid recovery of the inhibition of acetyl cholinesterase, see addendum 2.

Summary of operator exposure

1. Grain mixture

For the use as admixture in large scale automated hydraulic sprayer the estimated exposure is below the AOEL.
However, for small scale use i.e. knapsack application a comprehensive estimation is not available.

2. Structural treatment

For the structural treatment, the estimated exposure exceeded the AOEL to a great extent according to calculations based on an HSE model.
Therefore, a biomonitoring study was conducted and submitted by the notifier. Ten professional operators were evaluated and the exposure ranged from 4-157%. However, the study has some major drawbacks. For instance, the lack of scientific validation of the methods used to determine the biological marker for pirimiphos-methyl.

Worker exposure

Empty stores are expected to be treated with Actellic 50EC several weeks before harvest and then to remain closed during this period, with no access required. Workers are expected to wear PPE when handling treated grain and estimated exposure is probably below the AOEL

Bystander exposure

Bystanders are unlikely to be exposed to pirimiphos-methyl from applications of Actellic 50EC, such applications being made in a closed area (grain stores) with restricted access.

3. Residues

3.1. Nature and magnitude of residues in plant

3.1.1. Primary crops

Metabolism studies were conducted on stored grain where pyrimidinyl labelled pirimiphos-methyl was applied to maize, wheat and rice grain prior to storage.

In the study on maize grain the total radioactive residue (TRR) on the grain declined to circa 50% of the initial radioactivity during the first 12 weeks storage time, only a small decrease (additional 5%) occurred between 12 und 24 weeks storage. The majority (*ca* 90%) of the residue remained extractable over the storage period. At both sampling time points most of the recovered radioactivity was parent (*ca* 70 %). The main metabolite identified was R046382 amounting to 10 % TRR and 20% TRR at week 12 und 24, respectively. The other metabolites were hydroxypyrimidine compounds and did not individually exceed 6% of the TRR. The unknown radioactivity (12-21% TRR) was multi component.

In two further studies wheat and rice grain with different moisture content was treated with pirimiphos-methyl applied at two dose rates as a dust formulation or as an emulsifiable concentrate, respectively. The results of the study indicated that during the storage time of up to 32 weeks pirimiphos-methyl was slowly degraded on grain surfaces by hydrolysis of the phosphorothioate ester to yield principally the main metabolite R046382. The rate of degradation, at constant temperature, was dependent on the grain moisture content, increasing at higher moisture contents. At the lower humidity (14%), after 32 weeks storage, pirimiphos-methyl accounted still for *ca* 80 % of the total radioctivity whereas on grain with high moisture content (18%) only *ca* 15%-20% of the radioactivity was found pirimiphos-methyl yet. Also levels of unextractable residues increased with time at higher moisture contents and amounted to 57% radioactivity after 32 weeks in wheat grain with high moisture whereas in grain with lower moisture only 8% radioactivity was unextractable.

The decline of pirimiphos-methyl and the pattern of degradation products were similar in all grains studied, even though the rate of decline strongly depended on the moisture content of grain. Unchanged pirimiphos-methyl was the major residue found in grain. The major metabolites were compound R046382 (2-10% and 2-40% of radioactive residues in grain with low and high moisture content, respectively), a conjugated form of compound R046382 which released compound R046382 after hydrolysis (1-10% of radioactive residues) and compound R035510 (up to *ca* 5% of radioactive residues). These breakdown products are hydroxypyrimidine compounds and not considered to be toxicologically significant. The only metabolite considered to be of toxicological significance due to its pyrimidine-dialkyl phosphorothioate structure was R036341[8] (6% of radioactive residues in maize, 5% in rice, *max* 15% in wheat). This metabolite was looked for in residue trials and processing studies and was shown to not form a significant part of the residue given the high levels of pirimiphos-methyl.

In a radiolabelled processing study where pirimiphos-methyl was added to flour and then baked into bread the majority of the residue (>80 %) remained as pirimiphos-methyl, the only breakdown

[8] R036341: *O*-2-ethylamino-6-methylpyrimidin-4-yl *O,O*-dimethylphosphorothioate

products were pyrimidine metabolites which had already been seen in the metabolism data. The residue in stored grain should therefore be defined as pirimiphos-methyl only.

Four residue trials on cereals were provided where pirimiphos-methyl was applied under commercial conditions using an EC formulation at the recommended rate of 0.004 kg a.s./tonne. Residues at day 0 were between 1.1 and 2.7 mg/kg. Higher residues (up to 3.2 mg/kg) were found at later time points, which was likely to be related to the difficulty in getting a representative sample of grain. The higher residues were used in the risk assessment. In processing studies residues were examined in bread flour, milled products, bran breakfast cereal, beer, oat products and biscuits. From these data processing factors can be derived.

For the structural treatment four residue trials were carried out for a representative range of grain stores treated with a single application at 100 g ai/100 m^2 using a directed spray. Grain was then introduced to the stores and samples were taken at various time intervals. Residues were all below LOQ (<0.05 mg/kg).

Available data on the stability of residues in frozen storage indicate that there is no unacceptable degradation of residues in samples stored for up to 2 years. Procedural recoveries were required as confirmatory data and were submitted in April 2004. After evaluation the RMS concluded there is no unacceptable degradation over a storage period of 2 years. The experts' meeting on residues (EPCO 15) agreed that the data requirement was fulfilled, but these data were not evaluated in an addendum.

3.1.2. SUCCEEDING AND ROTATIONAL CROPS

The proposed use pattern requires that pirimiphos-methyl is only used indoors on stored products. It is not anticipated that any exposure will occur to soil that will subsequently support secondary crops.

3.2. NATURE AND MAGNITUDE OF RESIDUES IN LIVESTOCK

Because significant amounts of pirimiphos-methyl residues were found in potential feeding stuff and pirimiphos-methyl is deemed to be fat-soluble (log Pow 3.9-4.2) metabolism studies in livestock are necessary. Therefore animal metabolism was investigated in ruminants and in poultry. In these studies pyrimidinyl labelled pirimiphos-methyl was orally administered to a lactating goat and to laying hens. The majority of administered radioactivity was excreted by both species via urine 78 % and faeces 11 % and excreta 98%, respectively. In the hen and goat fat the only significant residue was pirimiphos-methyl (up to 72% TRR). On analysis of the milk and egg yolk only a small amount of pirimiphos-methyl was found (4 and 10% TRR, respectively) whereas the major residues were compounds R035510 (32 and 34% TRR) and R004039[9] (14% and 11%, respectively). In offal and tissues of hens and goats and in the albumen no pirimiphos-methyl was present, and again, the pyrimidine metabolites R035510 and R004039 made up the majority of the radioactive residue. All other metabolites identified were also pyrimidine metabolites and were not present at significant levels. R035510 and R004039 are not considered toxicologically significant. Thus, the residue of concern is defined as pirimiphos-methyl for risk assessment and monitoring purposes.

[9] R004039: 2-amino-4-hydroxy-6-methylpyrimidine

In an animal feeding study four groups of three lactating cows were dosed at a rate of 0, 5, 15 and 50 mg/kg diet dry matter. Residues of pirimiphos-methyl in the milk did not exceed 0.01 mg/kg for the 1N feed group. Residues in all tissues did not exceed 0.01 mg/kg. A second study confirmed these results. In a hen study pirimiphos-methyl was fed to laying hens at a rate of 1, 4, 8 and 32 mg/kg diet as dry matter. The dosing continued for periods of 7 to 28 days. In the 1N dose group no residues were detected in the muscle or in eggs (<0.01 mg/kg). Hence, MRLs for animal products are proposed on LOQ level.

3.3. CONSUMER RISK ASSESSMENT

From the use of pirimiphos-methyl as a structural treatment to empty stores no residues above 0.05 mg/kg (LOQ) were found and therefore consumer exposure from the use of pirimiphos-methyl as a structural treatment is of no concern. The highest TMDI, based on calculations with residue levels at LOQ for cereals and products of animal origin, was found for the most vulnerable consumer subgroup of young children (UK infant, toddler) and does not exceed 40% of the ADI of 0.004 mg/kg bw. (See addendum 3)

With regard to the grain admixture use on wheat, oats and barley a refined intake assessment including median residue data (STMR) and, partly, cereal processing factors was carried out. The estimated daily intakes (IEDI/NEDI) for chronic exposure assessment have been presented by the RMS in the DAR (Table 7.24) and in addendum 2, respectively. However, for the WHO European diet model based on GEMS/Food consumption data the agreed reference body weight for adults is 60 kg rather than 70.1 kg used by RMS in the addendum 2. Therefore the daily intake for adults presented below is slightly higher than the estimate given by the RMS in the addendum.
The risk assessment is based on an ADI of 0.004 mg/kg bw, which was agreed on in the experts' meeting on toxicology (EPCO 14), derived from animal data supported by human data (Refer to 2.10). The intake estimates given below indicate the ADI being exceeded for all considered consumer subgroups.

Adults:	GEMS/Food European regional diet	*0.00548 mg/kg bw/ day*	137 % ADI
	UK diet model (PSD)	*0.01229 mg/kg bw/ day*	307 % ADI
Children:	UK diet model (PSD) (toddler)	*0.02639 mg/kg bw/ day*	660 % ADI

If further refinement of the risk assessment for all cereal grain uses supported (wheat, oats and barley) should be done, further barley and oat processing data would be necessary. However, due to the generally low consumption of barley and oat compared to wheat a crucial alteration of the results is not expected, if such processing data would become available.

Acute exposure estimates based on UK consumption data do not indicate any of the considered consumer subgroups being at risk. (*max* 33% ARfD /school children)

3.4. PROPOSED MRLS

For stored wheat, barley and oat grain and MRL of 5 mg/kg is proposed and for products of animal origin except poultry fat an MRL of 0.01* mg/kg (LOQ) is proposed. For poultry fat the proposed MRL is 0.01 mg/kg. The current CAC MRL for cereal grain is 10 mg/kg.

It is noted that with MRLs for grain at a level of 5 mg/kg or even 10 mg/kg consumer exposure above the toxicological reference values can not be excluded. Taking into account only the use of pirimiphos-methyl as a structural treatment, the proposed MRL by RMS for wheat, barley and oat grain is 0.05* mg/kg.

4. Environmental fate and behaviour

4.1. FATE AND BEHAVIOUR IN SOIL

4.1.1. ROUTE OF DEGRADATION IN SOIL

Use of pirimiphos methyl will be restricted to indoor use for storage facilities treatment and stored cereals after harvest. The product is not volatile; therefore, contamination of natural soils due to the proposed use of pirimiphos methyl may be precluded.
Studies to investigate the route of degradation in soil are not required.

4.1.2. PERSISTENCE OF THE ACTIVE SUBSTANCE AND THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

Use of pirimiphos methyl will be restricted to indoor use for storage facilities treatment and stored cereals after harvest. The product is not volatile; therefore, contamination of natural soils due to the proposed use of pirimiphos methyl may be precluded.
Studies to investigate the rate of degradation in soil are not required.

4.1.3. MOBILITY IN SOIL OF THE ACTIVE SUBSTANCE AND THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

Use of pirimiphos methyl will be restricted to indoor use for storage facilities treatment and stored cereals after harvest. The product is not volatile; therefore, contamination of natural soils due to the proposed use of pirimiphos methyl may be precluded.
Studies to investigate the mobility of degradation in soil are not required.

4.2. FATE AND BEHAVIOUR IN WATER

4.2.1. SURFACE WATER AND SEDIMENT

Use of pirimiphos methyl will be restricted to indoor use for storage facilities treatment and stored cereals after harvest. The product is not volatile; therefore, contamination of natural waters due to the proposed use of pirimiphos methyl may be precluded.
Studies to investigate the fate of pirimiphos methyl in surface water are not required. However, aqueous hydrolysis and photolysis was investigated and results are summarized in the physico

chemical and fate and behaviour sections of the DAR. No readily biodegradability test is available, the substance may be considered as not readily biodegradable.

4.2.2. POTENTIAL FOR GROUND WATER CONTAMINATION OF THE ACTIVE SUBSTANCE THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

Use of pirimiphos methyl will be restricted to indoor use for storage facilities treatment and stored cereals after harvest. The product is not volatile; therefore, contamination of ground waters due to the proposed use of pirimiphos methyl may be precluded.

4.3. FATE AND BEHAVIOUR IN AIR

Use of pirimiphos methyl will be restricted to indoor use for storage facilities treatment and stored cereals after harvest. Whereas, data available indicate that pirimiphos-methyl may be significantly volatilised from soil and leaf surfaces, concentrations of pirimiphos-methyl in the air compartment are expected to be negligible, due to short persistence in the atmosphere. Contamination of natural environments through volatilization and deposition should be avoided with adequate measures are to minimize the emissions from the storage facilities.

5. Ecotoxicology

5.1. RISK TO TERRESTRIAL VERTEBRATES

Studies on acute and dietary toxicity to birds were provided, but since pirimiphos-methyl is an insecticide for the treatment of structural surfaces in empty grain stores as well as complete or surface admixture to cereal grain in store, it is considered that birds will not be exposed. Therefore no risk assessment is required. A non GLP study on reproductive toxicity to birds, not conducted to a recognised protocol, was available. Since no exposure of birds is expected this study was not used for a risk assessment. The risk to birds from the intended use is considered to be low and no further consideration is needed.

Studies are available that indicate that the acute oral LD50 for the rat is 1414 mg a.s./kg bw and the reproductive NOAEL from the multi-generation reproduction rat study is 160 ppm. As for birds, no exposure is expected to wild mammals and hence risk should be low. Therefore no TER-values were calculated.

According to the UK Wildlife Incident Investigation Scheme (WIIS) there has been one incident involving pirimiphos-methyl from use in grain stores since 1984. This incident occurred in 1996 and involved 15 pipistrelle bats. The amount of pirimiphos-methyl present in the bat carcasses was considered to be significant and may have contributed to the death of these bats. Field investigations indicated that pirimiphos-methyl may have been used in a nearby grain store, however the bats were found in a grain store that had not been treated for 6 years.

If wildlife is excluded from buildings during treatment exposure will be negligible and the risk to birds and mammals is therefore concluded to be low.

5.2. RISK TO AQUATIC ORGANISMS

Pirimiphos-methyl is for use only in enclosed spaces, from which exposure to aquatic environments is unlikely. However, studies on toxicity to aquatic organisms were provided and used for the classification of the active substance. The LC_{50} for fish was derived from a study with the a.s. and found to be 0.20 mg a.s./L. The most sensitive species to pirimiphos-methyl was the *Daphnia magna* with a 48 h LC_{50} of 0.00021 mg a.s./L. The E_bC_{50} of 1.2 mg a.s./L for algae was derived in a study with the formulated product 'Actellic 25EC'. Studies on long-term/chronic toxicity to fish and *Daphnia magna* were available but not used for risk assessment.

No data is available to address bioconcentration. However since the use pattern of pirimiphos-methyl is limited to enclosed food storage areas exposure leading to bioconcentration of pirimiphos-methyl into the fatty tissues of fish is unlikely to occur. Thus, a fish bioconcentration study is not considered necessary.

It is concluded that the risk to aquatic organisms from the intended use is low. However, since the toxicity to *Daphnia magna* is very high it should be ensured that emissions are minimized to avoid deposition to the aquatic environment.

5.3. RISK TO BEES

No studies were provided to assess the toxicity of pirimiphos-methyl to honey bees. Since pirimiphos-methyl is for exclusive use in situations where bees are not likely to be exposed it is concluded that from the correct use the risk is low.

5.4. RISK TO OTHER ARTHROPOD SPECIES

No studies were provided to assess the toxicity of pirimiphos-methyl to non-target arthropods. Since pirimiphos-methyl use is limited to enclosed food storage areas non-target arthropods are not likely to be exposed and studies are not required. It is concluded that from the correct use of pirimiphos-methyl the risk to non-target arthropods is low.

5.5. RISK TO EARTHWOMS

The 14-day LC_{50} for *Eisenia foetida* was determined to be 419 mg a.s./kg soil, whilst the NOEC was 10 mg a.s./kg soil. The use pattern of pirimiphos-methyl will be limited to enclosed food storage areas, and therefore it is considered unlikely that soil will be contaminated from the correct use of 'Actellic 50EC'. Hence the risk to earthworms is considered low and no risk assessment is necessary.

5.6. RISK TO OTHER SOIL NON-TARGET ORGANISMS

No studies were provided to assess the toxicity of pirimiphos-methyl to other soil non-target organisms. It is considered unlikely that soil will be contaminated from the correct use of 'Actellic 50EC' and hence the risk is considered low and there is no need for either data or risk assessment for the proposed use.

5.7. RISK TO SOIL NON-TARGET MICRO-ORGANISMS

No studies were provided to assess the toxicity of pirimiphos-methyl to other soil non-target organisms. It is considered unlikely that soil will be contaminated from the correct use of 'Actellic 50EC' and hence the risk is considered low and there is no need for either data or risk assessment for the proposed use.

5.8. RISK TO OTHER NON-TARGET-ORGANISMS (FLORA AND FAUNA)

Due to the restricted pattern of use, it is considered unlikely that non-target flora and fauna are likely to come in to contact with pirimiphos-methyl and the risk is therefore considered low. Hence there is no need for either data or risk assessment for the proposed use.

5.9. RISK TO BIOLOGICAL METHODS OF SEWAGE TREATMENT

Due to the restricted pattern of use, it is considered unlikely that sewage treatment works are likely to be exposed to pirimiphos-methyl, however the RMS proposed that this risk is assessed at MS level.

6. Residue definitions

Soil

Definitions for risk assessment: Not applicable

Definitions for monitoring: Not applicable

Water

Ground water

Definitions for risk assessment: Not applicable

Definitions for monitoring: Not applicable

Surface water

Definitions for risk assessment: Not applicable

Definitions for monitoring: Not applicable

Air

Definitions for risk assessment: pirimiphos-methyl (as default for human exposure after indoor use only)

Definitions for monitoring: pirimiphos-methyl (as default for indoor use only)

Food of plant origin

Definitions for risk assessment: pirimiphos-methyl (cereal grain in storage only)

Definitions for monitoring: pirimiphos-methyl (cereal grain in storage only)

Food of animal origin

Definitions for risk assessment: pirimiphos-methyl (cereal grain in storage only)

Definitions for monitoring: pirimiphos-methyl (cereal grain in storage only)

Overview of the risk assessment of compounds listed in residue definitions for the environmental compartments

Soil

Compound (name and/or code)	Persistence	Ecotoxicology
Contamination of soil compartment precluded for the proposed uses.	No assessment required; no assessment performed.	No assessment required; no assessment performed.

Ground water

Compound (name and/or code)	Mobility in soil	> 0.1 µg / L 1m depth for the representative uses (at least one FOCUS scenario or relevant lysimeter)	Pesticidal activity	Toxicological activity	Ecotoxicological activity
Contamination of soil compartment is precluded for the proposed uses.	No assessment required; no assessment performed.	No assessment required; no assessment performed.	No assessment required; no assessment performed.	No assessment required; no assessment performed.	No assessment required; no assessment performed.

Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Contamination of surface water compartment is precluded for the proposed uses.	No assessment required; no assessment performed.

Air

Compound (name and/or code)	Toxicology
Pirimiphos-methyl As default, contamination of air compartment precluded for the proposed uses.	No assessment required; no assessment performed.

LIST OF STUDIES TO BE GENERATED,-STILL ONGOING OR AVAILABLE BUT NOT PEER REVIEWED

- Procedural recoveries for study on stability of residues in frozen storage are required as confirmatory data (relevant for all representative uses evaluated; already submitted by the notifier in April 2004; no addendum was produced but a statement was included in the evaluation table by RMS and EPCO 15 agreed that the data requirement was fulfilled, refer to point 3.1.1)

CONCLUSIONS AND RECOMMENDATIONS

Overall conclusions

The conclusion was reached on the basis of the evaluation of the representative uses as insecticide as proposed by the notifier which comprises spraying to wheat, barley and oats grains during storage and treatment for structural surfaces in empty grain stores at an application rate up to of 4 g pirimiphos-methyl per tonne and 50 g per 100 m², respectively. Pirimiphos-methyl can be used as insecticide and acaricide.

The representative formulated product for the evaluation was "Actellic 50EC", an emulsifiable concentrate (EC), registered in several countries in Europe.

Adequate methods are available to monitor all compounds given in the respective residue definition. Residues in food of plant and animal origin can be determined with a multi-method. For the other matrices only single methods are available to determine residues of pirimiphos-methyl.

Sufficient analytical method as well as methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection product are possible.

Pirimiphos-methyl is extensively metabolised in rats. The acute oral toxicity is moderate i.e. LD_{50} 1414 mg/kg bw and of low inhalatory and dermal toxicity, LC_{50} > 4.7 mg/L air and LD_{50} > 2000 mg/kg bw, respectively. Pirimiphos-methyl was slightly irritating to skin and eye as well as induced mild sensitization. **Classification for acute toxicity is needed and the proposed risk phrase is: Xn; R22 "Harmful if swallowed".**

Generally, the main effect is inhibition of acetyl cholinesterase activity. The short term NOAELs are 0.5 and 2 mg/kg bw/day, from the 2-year dog study, based on inhibition of brain cholinesterase activity at the 12-month or 13-weeek time point, respectively. Pirimiphos-methyl was not genotoxic.

No carcinogenic potential was evident in the mouse. Some rare brain and pancreatic tumours were seen at 12.6 mg/kg bw/day (highest dose level) in a rat study of old date. Although within historical control range it is not possible to discount the assumption of a carcinogenic potential at higher dose levels. The NOAEL is 0.4 mg/kg bw/day. The experts agreed with a precautionary approach to propose **Xn; R40 "Limited evidence of a carcinogenic effect"**.

There were no direct effects on reproductive performance or fertility observed. Evidence of foetotoxicity, shifted pelvic position, was present at a high dose level, 48 mg/kg bw/day. The effect is rather uncommon and the experts concluded that this finding was a variation and not a malformation and classification of R63 was not proposed.
Two studies on human volunteers are reported, both from 1976, which were considered as scientifically valid by the experts.
The ADI is 0.004 mg/kg bw/day based on the 2-yr studies from rat and dog with an overall safety factor of 100 (supported by human data) applied. **The AOEL is 0.02 mg/kg bw/day** based on the 2-yr dog study (time point 13 weeks) and the 13-week neurotoxicity study in the rat with the safety factor of 100 applied, supported by human data. **The ARfD is 0.15 mg/kg bw**, safety factor 100.
The dermal absorption value is 1% for the concentrate and 10% for the dilution. The representative formulation Actellic 50EC is used as admixture and for structural treatment. **The estimated exposure for admixture, large scale automated treatment, is below the AOEL. However, based on available data for structural treatment the estimated operator exposure is above the AOEL.**

The decline of pirimiphos-methyl and the pattern of degradation products were similar in stored grain and after processing, even though the rate of decline strongly depended on the moisture content of the grain. Unchanged pirimiphos-methyl was the major residue found in grain and processed cereal products. Main metabolites were hydroxypyrimidine compounds, whereof 90% accounted for R046382. The only metabolite considered to be of toxicological significance was R036341. This metabolite was looked for in residue trials and processing studies and was shown to not form a significant part of the residue given the high levels of pirimiphos-methyl.
Pirimiphos-methyl is classified as fat soluble. However, if grain treated according to the cGAP is fed to livestock animals no residues above the limit of quantification (LOQ) are expected to occur in food of animal origin.
Chronic consumer exposure from the use of pirimiphos-methyl as a structural treatment to empty stores is of no concern. **With regard to chronic consumer exposure from the grain admixture use, the ADI is exceeded for all considered consumer subgroups.** An acute dietary risk for consumers exposed to pirimiphos-methyl residues on wheat, barley and oat grain is not expected from both uses evaluated.

Use of pirimiphos methyl will be restricted to indoor use for storage facilities treatment and stored cereals after harvest. Concentrations of pirimiphos-methyl in the air compartment are expected to be negligible, due to low volatility and short persistence in the atmosphere. Contamination of natural environments (soils and surface waters) through volatilization and deposition may be precluded.
Studies to investigate the fate of pirimiphos methyl in the different environmental compartments are not required. However, aqueous hydrolysis and photolysis was investigated and results are summarized in the physico chemical and fate and behaviour sections of the DAR. No readily biodegradability test is available, the substance may be considered as not readily biodegradable. Whereas, data available indicate that pirimiphos-methyl may be significantly volatilised from soil and leaf surfaces, concentrations of pirimiphos-methyl in the air compartment are expected to be

negligible, due to short persistence in the atmosphere. Contamination of natural environments through volatilization and deposition should be avoided with adequate measures to minimize the emissions from the storage facilities.

The risk to birds, wild mammals, aquatic organisms, bees and non-target arthropods, soil micro- and micro organisms, including earthworms, non-target plants and biological methods for sewage treatment is considered low based on the use pattern of pirimiphos-methyl which is limited to enclosed food storage areas.

Particular conditions proposed to be taken into account to manage the risk(s) identified

- Only indoor uses (storage) have been evaluated as representative uses. The risk from other uses (outdoor, greenhouse) has not been assessed.
- Additional PPE is needed in order to estimate operator exposure below the AOEL for admixture use (refer to point 2.12).

Critical areas of concern

- No repeated study on inhalation exposure is presented. Although pirimiphos-methyl is not toxic during acute exposure, attention should be paid since the formulation is intended for indoor use.
- Additional PPE should be considered for the grain admixture use. Only large scale use should be considered.
- Based on available data, the estimated exposure for structural treatment exceeds the AOEL even when respiratory personal equipment (RPE) is added.
- No estimate for small scale use, knap-sack sprayer, is provided, to be considered at Member State level.
- Risk for consumers identified since the chronic intake of pirimiphos-methyl residues from the grain admixture use is above the ADI.

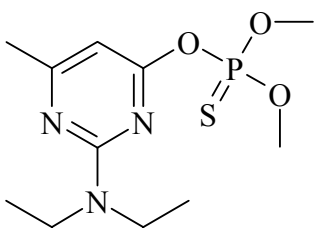
APPENDIX 1 – LIST OF ENDPOINTS FOR THE ACTIVE SUBSTANCE AND THE REPRESENTATIVE FORMULATION

(Abbreviations used in this list are explained in appendix 2)

Appendix 1.1: Identity, Physical and Chemical Properties, Details of Uses, Further Information

Active substance (ISO Common Name) ‡	Pirimiphos-methyl
Function (e.g. fungicide)	Insecticide
Rapporteur Member State	United Kingdom
Co-rapporteur Member State	--

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	*O*-2-diethylamino-6-methylpyrimidin-4-yl *O*,*O*-dimethyl phosphorothioate
Chemical name (CA) ‡	*O*-[2-(diethylamino)-6-methyl-4-pyrimidinyl] *O*,*O*-dimethyl phosphorothioate
CIPAC No ‡	239
CAS No ‡	29232-93-7
EEC No (EINECS or ELINCS) ‡	249-528-5
FAO Specification ‡ (including year of publication)	AGP: CP/221 (1998) 880 g/kg ± 20 g/kg (239/a/TC/S 1988)
Minimum purity of the active substance as manufactured ‡ (g/kg)	880 g/kg
Identity of relevant impurities (of toxicological, environmental and/or other significance) in the active substance as manufactured (g/kg)	None
Molecular formula ‡	$C_{11}H_{20}N_3O_3PS$
Molecular mass ‡	305.4
Structural formula ‡	

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Physical-chemical properties (Annex IIA, point 2)

Melting point (state purity) ‡	21 °C (purity 99.6%)
Boiling point (state purity) ‡	Not applicable
Temperature of decomposition	Decomposition occurred at 120 °C (purity 93.5%)
Appearance (state purity) ‡	Clear liquid 99.6% Pale yellow clear liquid 93.5%
Relative density (state purity) ‡	1.17 g/cm^3 @ 20 °C (purity 99.6%)
Surface tension	62.9 mN/m @ 20 °C
Vapour pressure (in Pa, state temperature) ‡	2.0 x 10^{-6} kPa @ 20 °C
Henry's law constant (Pa m^3 mol $^{-1}$) ‡	6.08 x 10^{-5} kPa m^3/mol
Solubility in water ‡ (g/l or mg/l, state temperature)	pH 7: 10 mg/L pH 5: 11 mg/L pH 9: 9.7 mg/L
Solubility in organic solvents ‡ (in g/l or mg/l, state temperature)	At 20 °C solubility is > 250 g/kg for xylene, 1,2-dichloroethane, methanol, acetone and ethyl acetate.
	Solubility at 20 °C is 249 g/kg solution in n-heptane
Partition co-efficient (log POW) ‡ (state pH and temperature)	log Pow at 20 °C is 3.9 in water buffered at pH 4 and 4.2 in purified water and water buffered at pH 5 and 7.
Hydrolytic stability (DT50) ‡ (state pH and temperature)	The DT_{50} at 25 °C was determined to be 2, 7, 117 and 75 days at pH 4, 5, 7 and 9 respectively. Two degradation compounds were determined as *O*-2-diethyl amino-6-methylpyrimidin-4-yl *O*-methyl phosphorothioate and 2-diethylamino-6-methylpyrimidin-4-ol. (R402186, R046382)
Dissociation constant ‡	4.30 @ 20°C
UV/VIS absorption (max.) ‡ (if absorption > 290 nm state ε at wavelength)	Absorbance >290 nm. The molar extinction coefficients in methanol are 301 nm = 3.69 x 10^3, 270 nm = 142 x 10^3, 247 nm = 2.24 x 10^4 and 220 nm = 3.39 x 10^3 L M-1 cm^{-1}
Photostability (DT50) ‡ (aqueous, sunlight, state pH)	The test solutions were continuously irradiated using light from a xenon arc lamp which was filtered to give a spectral distribution close to that of natural sunlight. Samples were irradiated for defined periods up to the equivalent of approximately 4.12 hours Florida Summer Sunlight and maintained at 25 ± 1 °C. Duplicate samples were analysed at approximately 0, 0.5, 1.1, 1.7, 2.5 and 4.1 hours of Florida

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

	Summer Sunlight. Duplicate dark control samples were also prepared and maintained at 25 ± 1 °C for the duration of the irradiation, and analysed at the final sampling time. Degraded extensively - estimated DT_{50} 0.46 and 0.47 hours at pH 5 and 7 respectively.
Quantum yield of direct phototransformation in water at Σ > 290 nm ‡	0.17 at pH 4, 0.24 at pH 7 and 0.26 at pH 9 following irradiation at 313 +/- 10 nm in buffered aqueous acetonitrile (75/25 at 20°C)
Flammability ‡	Not applicable - the active substance is a liquid at room temperature
Explosive properties ‡	Technical material not expected to be explosive - does not contain any bond groupings known to confer explosive properties. The exothermic heat of decomposition measured by DSC was approximately 200 J/g which supports the structure assessment

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

List of representative uses evaluated*

Crop and/ or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment (L/tonne, kg as/tonne)			PHI (days) (l)	Remarks (m)
					Type (d-f)	Conc. of as (i)	Method Kind (f-h)	Growth stage & season (j)	Number min max (k)	Interval between applica-tions (min)	kg as/hL min max	water L/t min max	kg as/t min max		
Wheat, Barley, Oats	EU	Actellic 50EC	I	Pests of stored grain	EC	500	Spray	After harvest	1	-	Up to 0.53	1	0.004	-	[1]
Structural treatment	EU	Actellic 50EC	I	Pests of stored grain	EC	500	Spray	Before storage	1	-	Up to 2.0	-	-	-	0.05 kg as/100m^2 [2]

[1] Chronic exposure of consumers above ADI, high risk identified in section 3
[2] Operator exposure above the AOEL

Remarks:				
	*	Uses for which risk assessment could not been concluded due to lack of essential data are marked grey	(h)	Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated
	(a)	For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)	(i)	g/kg or g/L
	(b)	Outdoor or field use (F), glasshouse application (G) or indoor application (I)	(j)	Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
	(c)	*e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds		
	(d)	*e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)	(k)	The minimum and maximum number of application possible under practical conditions of use must be provided
	(e)	GCPF Codes - GIFAP Technical Monograph No 2, 1989		
	(f)	Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench	(l)	PHI - minimum pre-harvest interval
	(g)	All abbreviations used must be explained	(m)	Remarks may include: Extent of use/economic importance/restrictions

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.2: Methods of Analysis

Analytical methods for the active substance (Annex IIA, point 4.1)

Technical as (principle of method)	GC-FID on a fused silica capillary column
Impurities in technical as (principle of method)	1) GC-FID on a fused silica capillary column. 2) HPLC with refractive index detection. 3) Karl Fischer method for water.
Plant protection product (principle of method)	Formulations were extracted with chloroform or acetone, pirimiphos-methyl content determined by GC-FID.

Analytical methods for residues (Annex IIA, point 4.2)

Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	The multi method (DFG S19) for pirimiphos-methyl is as follows. Pirimiphos-methyl was extracted with acetone/hexane and was analysed by GC with either thermionic or mass selective detector. The LOQ for monitoring purposes is 0.05 mg/kg. The method was validated on high water content, dry, acidic and oily matrices.
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	The method for monitoring is the DFG S19 method (GC-MS). The LOQ for monitoring purposes is 0.01 mg/kg.
Soil (principle of method and LOQ)	No residue definition is proposed Soil was extracted with acetone and 1M ammonium chloride solution and analysed by GC-MS. The LOQ was 0.01 mg/kg
Water (principle of method and LOQ)	No residue definition is proposed Water samples were loaded onto a C18 extraction column which was then eluted with acetonitrile and methanol. The analyte was analysed by GC-TSD with a limit of determination of 0.1 µg/l. The surface water method was GC-MS. The target ion was m/z 290 with qualifier ions m/z 276 and 305.
Air (principle of method and LOQ)	Tenax sampling tubes were used for the extraction of pirimiphos-methyl from air, the limit of determination was 0.003 mg/m^3.
Body fluids and tissues (principle of method and LOQ)	Not required, as pirimiphos-methyl is not classified as toxic or very toxic.

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Classification and proposed labelling (Annex IIA, point 10)

with regard to physical/chemical data	None

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.3: Impact on Human and Animal Health

Absorption, distribution, excretion and metabolism in mammals (Annex IIA, point 5.1)

Rate and extent of absorption ‡	Extensive (>80%) and relatively rapid
Distribution ‡	No data at Cmax but likely to be extensive
Potential for accumulation ‡	Some residues in fat following high doses, otherwise <2% of radiolabel in carcass at day 4
Rate and extent of excretion ‡	Extensive, primarily in urine; *ca* 70% excretion in 12h sample. Biliary component (>10%).
Metabolism in animals ‡	Extensively metabolised with no parent found in either urine or bile, primarily via cleavage of phosphorus-pyrimidine bond (at least 20 fractions).
Toxicologically significant compounds ‡ (animals, plants and environment)	Parent, metabolites containing the pyrimidine-dialkyl phosphorothioate structure, and their oxons

Acute toxicity (Annex IIA, point 5.2)

Rat LD50 oral ‡	1414 mg/kg bw **Xn; R22**
Rat LD50 dermal ‡	>2000 mg/kg bw
Rat LC50 inhalation ‡	>4.7 mg/L (4 hours, nose only)
Skin irritation ‡	Slightly irritating (no classification proposed)
Eye irritation ‡	Slightly irritating (no classification proposed)
Skin sensitization ‡ (test method used and result)	Weak response (Magnusson and Kligman test) - no classification proposed

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect ‡	Acetyl cholinesterase inhibition identified from 7 days onwards in a 2-yr dog study.
Lowest relevant oral NOAEL / NOEL ‡	2.0 mg/kg bw/day, 2-yr dog (time point 12 month) 0.5 mg/kg bw/day, 2-yr dog (time point 12 week)
Lowest relevant dermal NOAEL / NOEL ‡	No reliable data
Lowest relevant inhalation NOAEL / NOEL ‡	No data, not required

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Genotoxicity ‡ (Annex IIA, point 5.4)

.....	Positive bacterial mutation results in the literature not reproduced in a well performed unpublished study. Equivocal increases in SCE (questionable biological significance) but weight of *in vitro* evidence is negative. Negative *in vivo*.

Long term toxicity and carcinogenicity (Annex IIA, point 5.5)

Target/critical effect ‡	Acetyl cholinesterase inhibition, 2-yr rat.	
Lowest relevant NOAEL / NOEL ‡	0.4 mg/kg bw/day in 2 year rat	
Carcinogenicity ‡	Negative in mice. Equivocal brain and pancreas tumour incidence in poorly reported rat study.	**R40**

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction target / critical effect ‡	Not toxic to reproduction (rat)
Lowest relevant reproductive NOAEL / NOEL ‡	Parental: 1 mg/kg bw/day on cholinesterase inhibition. Reproduction: >12 mg/kg bw/day (highest dose) Offspring: 12 mg/kg bw/day (highest dose)
Developmental target / critical effect ‡	Not teratogenic. Shifted pelvic position at a maternally toxic dosage (cholinesterase inhibition) in rabbits (borderline effect, considered to be a variation rather than a malformation)
Lowest relevant developmental NOAEL / NOEL ‡	Maternal: 12 mg/kg bw/day RBC cholinesterase inhibition in rabbits. Developmental: 24 mg/kg bw/day (pelvic shift) in rabbits. Developmental NOAEL in a limited rat study was >150 mg/kg bw/day (highest dose).

Neurotoxicity / Delayed neurotoxicity ‡ (Annex IIA, point 5.7)

Acute study (rat)	NOAEL 15 mg/kg bw based on brain and erythrocyte cholinesterase inhibition
Short term study (rat)	NOAEL 2.1 mg/kg bw/day based on brain and erythrocyte cholinesterase inhibition, 13-week study
Delayed neurotoxicity	Does not induce delayed neurotoxicity

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Other toxicological studies ‡ (Annex IIA, point 5.8)

Human volunteer studies	NOAEL 0.25 mg/kg bw/day based on no effects on acetyl cholinesterase activity in 28- and 56-day studies from 1976

Medical data ‡ (Annex IIA, point 5.9)

.....	Reports of signs/symptoms in operators rare (in UK) given extent of use

Summary (Annex IIA, point 5.10)	Value	Study	Safety factor
ADI ‡	0.004 mg/kg bw	2 year rat and dog studies supported by human data	100
AOEL ‡	0.02 mg/kg bw	2 year dog study at 12 weeks and 13 week neurotox rat study supported by human data	100
ARfD ‡ (acute reference dose)	0.15 mg/kg bw	Rat acute neurotox.	100

Dermal absorption (Annex IIIA, point 7.3)

Actellic 50 (EC)	1% for concentrate 10% for dilution Based on *in vitro* studies (rat and human skin)

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Acceptable exposure scenarios (including method of calculation)

Operator	Grain admixture use Exposure estimates using UK POEM mixing and loading data indicate the grain admixture use of 'Actellic 50EC' via automated equipment is below the AOEL when PPE are worn (1.25 % of the AOEL). Structural treatment Estimates of exposure for an operator applying 'Actellic 50EC' as a structural treatment, based on UK HSE generic exposure data for remedial timber treatment in situ, are above the systemic AOEL when PPE are worn (median to worst case). Commercial 555 - 50 540 % Farm 185 - 16 845 % The operator exposure from the use of pirimiphos-methyl as a structural treatment based on higher tier biomonitoring data (study of questionable quality) using the 90th percentile value is within the AOEL of 0.02 mg/kg bw/day in 9 out of 10 study participants. Exposure of one of the biomonitoring participants exceeds (157%) the AOEL.
Workers	Empty stores are expected to be treated with 'Actellic 50EC' several weeks before harvest and then to remain closed during this period, with no access required. Workers are expected to wear PPE when handling treated grain. The risk to workers entering treated stores or from handling treated grain is considered to be within acceptable levels.
Bystanders	Bystanders are unlikely to be exposed to pirimiphos-methyl from applications of 'Actellic 50EC', such applications being made in a closed area (grainstores) with restricted access.

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Classification and proposed labelling (Annex IIA, point 10)

with regard to toxicological data	Xn
	R22 Harmful if swallowed
	R40 Limited evidence of a carcinogenic effect
	S2 Keep out of the reach of children
	S23 Do not breathe spray
	S36/37 Wear suitable protective clothing and gloves
	S46 If swallowed seek medical advice immediately and show this container or label

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.4: Residues

Metabolism in plants (Annex IIA, point 6.1 and 6.7, Annex IIIA, point 8.1 and 8.6)

Plant groups covered	stored grain
Rotational crops	Not required
Plant residue definition for monitoring	pirimiphos-methyl
Plant residue definition for risk assessment	pirimiphos-methyl
Conversion factor (monitoring to risk assessment)	-

Metabolism in livestock (Annex IIA, point 6.2 and 6.7, Annex IIIA, point 8.1 and 8.6)

Animals covered	Hen and goat
Animal residue definition for monitoring	pirimiphos-methyl
Animal residue definition for risk assessment	pirimiphos-methyl
Conversion factor (monitoring to risk assessment)	-
Metabolism in rat and ruminant similar (yes/no)	Yes
Fat soluble residue: (yes/no)	Yes

Residues in succeeding crops (Annex IIA, point 6.6, Annex IIIA, point 8.5)

.....	Not required

Stability of residues (Annex IIA, point 6 introduction, Annex IIIA, point 8 introduction)

.....	Residues were stable in tomato, lettuce, carrot, barley, and olive for a period of 2 years.

Residues from livestock feeding studies (Annex IIA, point 6.4, Annex IIIA, point 8.3)

Intakes by livestock ≥ 0.1 mg/kg diet/day:	Ruminant: yes mg/kg	Poultry: yes mg/kg
Muscle	≤ 0.01	≤ 0.01
Liver	≤ 0.01	≤ 0.01
Kidney	≤ 0.01	≤ 0.01
Fat	≤ 0.01	0.01
Milk	≤ 0.01	
Eggs		≤ 0.01

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Summary of critical residues data (Annex IIA, point 6.3, Annex IIIA, point 8.2)

Crop	Northern or Mediterranean Region	Trials results relevant to the critical GAP (a)	Recommendation/ comments	MRL	STMR (b)
Cereal grain	N	1.1, 2.5, 2.8, 3.2	Stored grain treatment	5	2.65
Cereal grain	N/S	4 x <0.05	Structural treatment	0.05*	<0.05

(a) Numbers of trials in which particular residue levels were reported *e.g.* 3 x <0.01, 1 x 0.01, 6 x 0.02, 1 x 0.04, 1 x 0.08, 2 x 0.1, 2 x 0.15, 1 x 0.17

(b) Supervised Trials Median Residue *i.e.* the median residue level estimated on the basis of supervised trials relating to the critical GAP

Consumer risk assessment (Annex IIA, point 6.9, Annex IIIA, point 8.8)

ADI	0.004 mg/kg bw
TMDI (European Diet) (% ADI)	Not calculated; see IEDI and NEDI
IEDI (%ADI) NEDI (%ADI)	WHO/FAO: 137% (adult) for the grain treatment UK: 307% (adult) for the grain treatment UK: 660% (toddler) for the grain treatment UK: 7-36 % (range for UK population subgroups) for the structural treatment
Factors included in IEDI Factors included in NEDI	STMR, Processing factor for wholemeal bread STMR
ARfD	0.15 mg/kg bw
Acute exposure (% ARfD)	Max 33 %

Processing factors (Annex IIA, point 6.5, Annex IIIA, point 8.4)

Crop/processed crop	Number of studies	Transfer factor	% Transference *
White flour	3	0.24	-
Wholemeal flour	3	0.68	-
White bread	3	0.14	-
Wholemeal bread	3	0.57	-
Rolled Oats	1	0.18	-
Bran	2	4	-

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Crop/processed crop	Number of studies	Transfer factor	% Transference *
Bran breakfast cereal	1	0.44	-
Biscuits from white flour	1	0.22	-

* Calculated on the basis of distribution in the different portions, parts or products as determined through balance studies

Proposed MRLs (Annex IIA, point 6.7, Annex IIIA, point 8.6)

Wheat, barley and oat grain	5 mg/kg
Wheat, barley and oat grain (residues from the structural treatment)	0.05* mg/kg
Poultry fat	0.01 mg/kg
All other animal matrices	0.01* mg/kg

*) LOQ

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.5: Fate and Behaviour in the Environment

Route of degradation (aerobic) in soil (Annex IIA, point 7.1.1.1.1)

Mineralization after 100 days ‡	Data were submitted but not used for risk assessment.
Non-extractable residues after 100 days ‡	Data were submitted but not used for risk assessment.
Relevant metabolites - name and/or code, % of applied ‡ (range and maximum)	Data were submitted but not used for risk assessment.

Route of degradation in soil - Supplemental studies (Annex IIA, point 7.1.1.1.2)

Anaerobic degradation ‡	Data were submitted but not used for risk assessment.
Soil photolysis ‡	No data submitted or required.

Rate of degradation in soil (Annex IIA, point 7.1.1.2, Annex IIIA, point 9.1.1)

Method of calculation	Data were submitted but not used for risk assessment.
Laboratory studies ‡ (range or median, with n value, with r^2 value)	DT_{50lab} (20°C, aerobic): DT_{90lab} (20°C, aerobic): DT_{50lab} (10°C, aerobic): DT_{50lab} (20°C, anaerobic):
	degradation in the saturated zone: ‡ No data submitted or required.
Field studies ‡ (state location, range or median with n value)	DT_{50f}: No data submitted or required. DT_{90f}:
Soil accumulation and plateau concentration ‡	

Soil adsorption/desorption (Annex IIA, point 7.1.2)

K_f /K_{oc} ‡ K_d ‡ pH dependence ‡ (yes / no) (if yes type of dependence)	Data were submitted but not used for risk assessment.

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Mobility in soil (Annex IIA, point 7.1.3, Annex IIIA, point 9.1.2)

Column leaching ‡	No data submitted or required.
Aged residues leaching ‡	No data submitted or required.
Lysimeter/ field leaching studie ‡	No data submitted or required.

PEC (soil) (Annex IIIA, point 9.1.3)

Parent

Method of calculation	PEC estimates are not required.
Application rate	

PEC$_{(s)}$ (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial				
Short term 4h				
2d				
4d				
Long term 7d				
28d				
50d				
100d				

Metabolite

Method of calculation	PEC estimates are not required.
Application rate	

PEC$_{(s)}$ (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial				
Short term 24h				
2d				
4d				

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

PEC$_{(s)}$ (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Long term 7d 28d 50d 100d				

Route and rate of degradation in water (Annex IIA, point 7.2.1)

Hydrolysis of active substance and relevant metabolites (DT$_{50}$) ‡ (state pH and temperature)	Data were submitted but not used for risk assessment. pH_____: pH_____:
Photolytic degradation of active substance and relevant metabolites ‡	Data were submitted but not used for risk assessment.
Readily biodegradable (yes/no)	No data submitted or required.
Degradation in water/sediment - DT$_{50}$ water ‡ - DT$_{90}$ water ‡ - DT$_{50}$ whole system ‡ - DT$_{90}$ whole system ‡	No data submitted or required.
Mineralization	
Non-extractable residues	
Distribution in water / sediment systems (active substance) ‡	
Distribution in water / sediment systems (metabolites) ‡	

PEC (surface water) (Annex IIIA, point 9.2.3)

Parent

Method of calculation	PEC estimates are not required.
Application rate	
Main routes of entry	

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

PEC$_{(sw)}$ (µg / l)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial				
Short term 4h 2d 4d				
Long term 7d 14d 21d 28d 42d				

Metabolite

Method of calculation	PEC estimates are not required.
Application rate	
Main routes of entry	

PEC$_{(sw)}$ (µg / l)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial				
Short term 24h 2d 4d				
Long term 7d 14d 21d 28d 42d				

PEC (sediment)

Parent

Method of calculation	PEC estimates are not required.
Application rate	

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

PEC$_{(sed)}$ (µg / kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial				
Short term				
Long term				

Metabolite

Method of calculation	PEC estimates are not required.
Application rate	

PEC$_{(sed)}$ (µg / kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial				
Short term				
Long term				

PEC (ground water) (Annex IIIA, point 9.2.1)

Method of calculation and type of study (*e.g.* modelling, monitoring, lysimeter)	PEC estimates are not required.
Application rate	

PEC$_{(gw)}$

Maximum concentration	
Average annual concentration (Results quoted for modelling with FOCUSgw scenarios, according to FOCUS guidance)	

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

PEC(gw) - FOCUS modelling results

Model /Crop	Scenario	Parent (µg/l)	Metabolite (µg/l)		
			1	2	3

Fate and behaviour in air (Annex IIA, point 7.2.2, Annex III, point 9.3)

Direct photolysis in air ‡	No data submitted or required.
Quantum yield of direct phototransformation	No data submitted or required.
Photochemical oxidative degradation in air ‡	Data were submitted but not used for risk assessment.
Volatilization ‡	Data were submitted but not used for risk assessment.

PEC (air)

Method of calculation	PEC estimates are not required.

$PEC_{(a)}$

Maximum concentration	PEC estimates are not required.

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Definition of the Residue (Annex IIA, point 7.3)

Relevant to the environment	**Soil** Definitions for risk assessment and monitoring: Not applicable **Water** **Ground water** Definitions for risk assessment and monitoring: Not applicable **Surface water** Definitions for risk assessment and monitoring: Not applicable **Air** Definitions for risk assessment: pirimiphos-methyl (as default for human exposure after indoor use only) Definitions for monitoring: pirimiphos-methyl (as default for indoor use only)

Monitoring data, if available (Annex IIA, point 7.4)

Soil (indicate location and type of study)	No data submitted or required.
Surface water (indicate location and type of study)	No data submitted or required.
Ground water (indicate location and type of study)	No data submitted or required.
Air (indicate location and type of study)	No data submitted or required.

Classification and proposed labelling (Annex IIA, point 10)

with regard to fate and behaviour data	None.

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.6: Effects on non-target Species

Effects on terrestrial vertebrates (Annex IIA, point 8.1, Annex IIIA, points 10.1 and 10.3)

Acute toxicity to mammals ‡	Data submitted but not used for risk assessment
Acute toxicity to birds ‡	Data submitted but not used for risk assessment
Dietary toxicity to birds ‡	Data submitted but not used for risk assessment
Reproductive toxicity to birds ‡	Data submitted but not used for risk assessment

Toxicity/exposure ratios for terrestrial vertebrates (Annex IIIA, points 10.1 and 10.3)

Pirimiphos-methyl formulated as Actellic 50EC is to be used in grain stores and as a result there will be negligible exposure of birds and mammals. Therefore, no toxicity:exposure ratios have been calculated.

Toxicity data for aquatic species (most sensitive species of each group) (Annex IIA, point 8.2, Annex IIIA, point 10.2)

Group	Test substance	Time-scale	Endpoint	Toxicity (mg/l)
Laboratory tests ‡				
Oncorhynchus mykiss	a.s.	96 hours	LC50	0.404 mg a.s./l
Oncorhynchus mykiss	a.s.	96 hours	LC50	0.20 mg a.s./l
Cyprinus carpio	a.s	96 hours	LC50	1.4 mg a.s./l
Daphnia magna	a.s.	48 hours	EC50	0.00021 mg a.s./l
Selenastrum capricornutum	a.s.	96 hours	EbC50	1.0 mg a.s./l
Oncorhynchus mykiss	'Actellic 25EC'	96 hours	LC50	1.01 mg form/l (equivalent to 0.266 mg a.s./l)
Cyprinus carpio	'Actellic 25EC'	96 hours	LC50	2.9 mg form/l (equivalent to 0.76 mg a.s./l)
Daphnia magna	'Actellic 50EC'	48 hours	EC50	0.00025 mg a.s./l
Selenastrum capricornutum	50% EC formulation	72 hours	EbC50	2.4 mg form/l (equivalent to 1.2 mg a.s./l)
Oncorhynchus mykiss	a.s.	28 days	EC50	Data submitted but not used for risk assessment
Daphnia magna	a.s.	21 days	NOEC	Data submitted but not used for risk assessment

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Microcosm or mesocosm tests
None submitted/required

Toxicity/exposure ratios for the most sensitive aquatic organisms (Annex IIIA, point 10.2)

Pirimiphos-methyl formulated as Actellic 50EC is to be used in grain stores, and as a result there will be negligible exposure of aquatic life, hence no toxicity:exposure ratios have been calculated.

Bioconcentration

Bioconcentration factor (BCF) ‡	No data submitted/required
Annex VI Trigger:for the bioconcentration factor	n.a.
Clearance time (CT_{50}) (CT_{90})	n.a.
Level of residues (%) in organisms after the 14 day depuration phase	n.a.

Effects on honeybees (Annex IIA, point 8.3.1, Annex IIIA, point 10.4)

Acute oral toxicity ‡	No data submitted/required
Acute contact toxicity ‡	No data submitted/required

Hazard quotients for honey bees (Annex IIIA, point 10.4)

Pirimiphos-methyl formulated as Actellic 50EC is to be used in grain stores, and as a result there will be negligible exposure of honeybees, therefore no hazard quotients have been calculated.

Effects on other arthropod species (Annex IIA, point 8.3.2, Annex IIIA, point 10.5)

No data have been submitted.

Pirimiphos-methyl formulated as Actellic 50EC is to be used in grain stores, and as a result there will be negligible exposure of non-target arthropods, therefore no risk assessment has been carried out.

Effects on earthworms (Annex IIA, point 8.4, Annex IIIA, point 10.6)

Acute toxicity ‡	Data submitted but not used for risk assessment
Reproductive toxicity ‡	No data submitted/required

Toxicity/exposure ratios for earthworms (Annex IIIA, point 10.6)

Pirimiphos-methyl formulated as Actellic 50EC is to be used in grain stores, and as a result there will be negligible exposure of earthworms, therefore no risk assessment has been carried out.

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Effects on soil micro-organisms (Annex IIA, point 8.5, Annex IIIA, point 10.7)

Nitrogen mineralization ‡	No data submitted/required
Carbon mineralization ‡	No data submitted/required

Pirimiphos-methyl formulated as Actellic 50EC is to be used in grain stores, and as a result there will be negligible exposure of aquatic life, therefore no toxicity:exposure ratios have been calculated.

Classification and proposed labelling (Annex IIA, point 10)

with regard to ecotoxicological data	R50 very toxic to aquatic organisms; R53 may cause long-term adverse effects in the aquatic environment; S60 This material and its container must be disposed of as hazardous waste; S61 Avoid release in the environment. Refer to special instructions/safety sheets

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

APPENDIX 2 – ABBREVIATIONS USED IN THE LIST OF ENDPOINTS

ADI	acceptable daily intake
AOEL	acceptable operator exposure level
ARfD	acute reference dose
a.s.	active substance
bw	body weight
CA	Chemical Abstract
CAS	Chemical Abstract Service
CIPAC	Collaborative International Pesticide Analytical Council Limited
d	day
DAR	draft assessment report
DM	dry matter
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
ε	decadic molar extinction coefficient
EC_{50}	effective concentration
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINKS	European List of New Chemical Substances
EMDI	estimated maximum daily intake
ER50	emergence rate, median
EU	European Union
FAO	Food and Agriculture Organisation of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	good agricultural practice
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GS	growth stage
h	hour(s)
ha	hectare
hL	hectolitre
HPLC	high pressure liquid chromatography or high performance liquid chromatography
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
K_{oc}	organic carbon adsorption coefficient
L	litre
LC	liquid chromatography
LC-MS	liquid chromatography-mass spectrometry
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LC_{50}	lethal concentration, median

LD_{50}	lethal dose, median; dosis letalis media
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification (determination)
µg	microgram
mN	milli-Newton
MRL	maximum residue limit or level
MS	mass spectrometry
NESTI	national estimated short term intake
NIR	near-infrared-(spectroscopy)
nm	nanometer
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
PEC	predicted environmental concentration
PEC_A	predicted environmental concentration in air
PEC_S	predicted environmental concentration in soil
PEC_{SW}	predicted environmental concentration in surface water
PEC_{GW}	predicted environmental concentration in ground water
PHI	pre-harvest interval
pK_a	negative logarithm (to the base 10) of the dissociation constant
PPE	personal protective equipment
ppm	parts per million (10^{-6})
ppp	plant protection product
r^2	coefficient of determination
RPE	respiratory protective equipment
STMR	supervised trials median residue
TER	toxicity exposure ratio
TMDI	theoretical maximum daily intake
UV	ultraviolet
WHO	World Health Organisation
WG	water dispersible granule
yr	year