European Food Safety Authority

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CONCLUSION ON PESTICIDE PEER REVIEW

Peer review of the pesticide risk assessment of the active substance pyriproxyfen[1]

(Question No EFSA-Q-2009-00239)

Issued on 21 July 2009

SUMMARY

Pyriproxyfen is one of the 79 substances of the third stage part A of the review programme covered by Commission Regulation (EC) No 1490/2002[2].

Pyriproxyfen was included in Annex I to Directive 91/414/EEC on 1 January 2009 pursuant to Article 11b of the Regulation (EC) No 1490/2002 (hereinafter referred to as 'the Regulation'). In accordance with Article 12a of the Regulation the European Food Safety Authority (EFSA) is required to deliver by 31 December 2010 its view on the draft review report submitted by the Commission of the European Communities (hereinafter referred to as 'the Commission') in accordance with Article 12(1) of the Regulation. This review report has been established as a result of the initial evaluation provided by the designated rapporteur Member State in the Draft Assessment Report (DAR). The EFSA therefore organised a peer review of the DAR. The conclusions of the peer review are set out in this report.

The Netherlands being the designated rapporteur Member State submitted the DAR on pyriproxyfen in accordance with the provisions of Article 10(1) of the Regulation, which was received by the EFSA on 24 November 2005. The peer review was initiated on 21 July 2006 by dispatching the DAR for consultation of the Member States and the sole notifier Sumitomo Chemical Agro Europe S.A. Subsequently, the comments received on the DAR were examined and responded by the rapporteur Member State in the reporting table. This table was evaluated by EFSA to identify the remaining issues which were agreed during a written procedure in September – October 2007. The identified issues as well as further information made available by the notifier upon request were evaluated in a series of scientific meetings with Member State experts in January 2009.

A final discussion of the outcome of the consultation of experts took place during a written procedure with the Member States in March 2009.

[1] For citation purposes: Conclusion on pesticide peer review regarding the risk assessment of the active substance pyriproxyfen. *EFSA Scientific Report* (2009) 336 1-99

[2] OJ L224, 21.08.2002, p.25, as amended by Regulation (EC) No 1095/2007 (OJ L246, 21.9.2007, p.19).

This conclusion was reached on the basis of the evaluation of the representative uses as an insecticide on protected tomato and aubergine[3] and field grown cotton. Full details of the GAP can be found in the list of end points attached as Appendix A.

The representative formulated product for the evaluation was 'Pyriproxyfen 10 EC', an emulsifiable concentrate (EC).

Adequate methods are available to monitor all compounds given in the respective residue definition. Residues in food of plant origin and in soil 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 pyriproxyfen. It should be noted that the residue definition for surface water is provisional.

Sufficient analytical methods 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. The maximum level of two impurities in the specification was not supported by the available data. However, it should be noted that the specification was accepted by mammalian toxicology. The biological activity of the two isomers that make up pyriproxyfen has not been concluded on. Some spectra data, relative density, Henry's law constant, water solubility and partition coefficient were identified as data gaps. It should be noted however that new studies were submitted to address these data gaps but these could not be taken into account in view of the restrictions concerning the acceptance of new studies after the submission of the DAR to EFSA, as laid down in Commission Regulation (EC) No. 1095/2007. Oxidising properties and details of the commercial packaging are outstanding issues for the formulated product.

With regard to the mammalian toxicology, pyriproxyfen was of low acute toxicity in all tested species, and was neither a skin nor eye irritant, nor a skin sensitizer. After repeated administration, the main target organ was the liver, and slight changes were also observed in the haematological parameters. Negative results were obtained in gene mutation, chromosome aberration and DNA repair tests *in vitro*, as well as *in vivo* in a micronucleus test. No evidence of a carcinogenic potential was observed in long-term studies in rats and mice. No adverse effects were observed in the reproductive parameters during a multigeneration study with rats. In the developmental toxicity studies, no teratogenic effect was observed but developmental effects were present in rats at maternal toxic doses. A severe maternal toxicity was observed in both species at the high dose level.

Considering the dog as the most sensitive species, the agreed Acceptable Daily Intake (ADI) was 0.1 mg/kg bw/day based on the 1-year dog study and with the use of a safety factor of 100. The same study was used to derive the Acceptable Operator Exposure Level (AOEL) with a correction for a limited oral absorption (40%), leading to a value of 0.04 mg/kg bw/day. Based on the low toxicity profile of pyriproxyfen, the derivation of an Acute Reference Dose (ARfD) was not considered necessary. The agreed dermal absorption values were 2.5% for the concentrate and 13% for the dilution. The exposure estimates for the operator are below the AOEL without the use of personal protective equipment during outdoor and indoor application in Northern Europe, the indoor application in Southern Europe requires the use of personal protective equipment in order to have an exposure level below the AOEL according to the Dutch model for greenhouse use.

[3] Also referred to in the DAR as egg plant

Metabolism of pyriproxyfen was studied in the categories fruit and oilseed crops. The studies indicated that pyriproxyfen was more extensively metabolised in cotton than in tomato. Total residues were low in cotton seed and no major compound could be identified. In tomato, however, the major residue was found to be pyriproxyfen, with some minor metabolites detected. Processing data indicated that pyriproxyfen residues did not decay to form any significant degradation product. On the basis of a confined rotational crop study and soil dissipation data it was concluded that significant residues in rotational crops are unlikely to occur. The residue definition for monitoring and risk assessment for the representative uses was proposed as pyriproxyfen alone.

A sufficient number of valid supervised residue trials with pyriproxyfen in tomato and cotton were submitted to support the respective notified uses. According to current guidance, the data on tomato can moreover be used to extrapolate to the notified use on aubergine. On the basis of the available residue data MRLs for pyriproxyfen of 0.3 mg/kg were proposed for tomato and aubergine, respectively, and at the limit of quantification (LOQ) of the analytical method of 0.01 mg/kg for cotton seed.

Residues in livestock feed are not expected to occur at significant levels. The only potential feed item used in current European feeding practice is cotton seed meal. However, residues in cotton seed and cotton seed meal were below the LOQ (0.01 mg/kg).

An estimate of the theoretical maximum daily intake (TMDI) of the consumer with the established MRLs resulted in chronic intakes well below the ADI (<2%) for all considered consumer groups including young children. Based on the low toxicity profile of pyriproxyfen an ARfD was considered not necessary. Therefore, an acute consumer risk assessment is not required.

In soil under aerobic conditions pyriproxyfen exhibits low to moderate persistence forming the minor soil metabolites 4'-OH-pyr[4] (accounting for up to 6.3% of applied radioactivity (AR)) which exhibits moderate persistence and PYPAC[5] (accounting for up to 8.6 % AR) which exhibits very low to moderate persistence. Mineralisation of both the phenoxyphenyl ring and 2,6-pyridyl labels to carbon dioxide accounted for 11-61% AR after 90-94 days. The formation of unextractable residues was a significant sink, accounting for 30-58 % AR after 90-122 days. Pyriproxyfen is immobile in soil, 4'-OH-pyr exhibits low to slight mobility in soil whilst PYPAC exhibits very high mobility. There was no indication that adsorption of either pyriproxyfen, 4'-OH-pyr or PYPAC was pH dependant.

In a sterile laboratory aqueous photolysis study the major metabolite PYPA[6] was formed accounting for up to 70% AR. However as the rate of photolytic decline of pyriproxyfen in this study was slower than in natural sediment water systems where viable microorganisms were present, combined with the information that pyriproxyfen would be expected to partition rapidly to sediments in natural systems, it was concluded that under field conditions PYPA would not be expected to be formed in significant amounts. In dark natural sediment water systems pyriproxyfen partitioned to sediment and degraded exhibiting low persistence, to the metabolites 4'-OH-pyr in sediment, which exhibited very low to low persistence, PYPAC in water, which exhibited moderate to medium persistence, and to DPH-pyr[7] in water. The terminal metabolite, CO_2, was a sink in the material balance accounting for a maxima of 11-52 % AR at 100 days (study end). Unextracted sediment residues were a major sink

[4] 4'-OH-pyr: 4-(4'-hydroxyphenoxyphenyl) (RS)-2-(2-pyridyloxy)propyl ether
[5] PYPAC: (RS)-2-(2-pyridyloxy)propionic acid
[6] PYPA: (RS)-2-(2-pyridyloxy)propyl alcohol
[7] DPH-pyr: 4-hydroxyphenyl (RS)-2-(2-pyridyloxy)propyl ether

representing 31-51 % AR at study end. The necessary surface water and sediment exposure assessments were appropriately carried out using the agreed FOCUS scenarios approach for pyriproxyfen at steps 1-3. For the metabolites 4'-OH-Pyr, PYPAC, DPH-Pyr appropriate FOCUS step 1 and 2 calculations were carried out. These values are the basis for the risk assessment discussed in this conclusion.

The potential for groundwater exposure from the applied for intended uses by pyriproxyfen and the metabolites 4'-OH-pyr and PYPAC above the parametric drinking water limit of 0.1 µg/L was concluded to be low in geoclimatic situations that are represented by all the FOCUS groundwater scenarios when a single crop per calendar year is cultivated.

The risk from uptake of pyriproxyfen from the diet, drinking water and secondary poisoning was assessed as low for birds and mammals for all intended uses. Pyriproxyfen was assessed as very toxic to aquatic organisms and not readily biodegradable (R50/53). A higher tier microcosm study was provided to address the risk to aquatic organisms. As insects were missing in the microcosm, a data gap was identified for the notifier to address the risk to aquatic insects before the aquatic risk assessment could be finalised for all intended uses. The application of an assessment factor to the microcosm endpoint should be considered when data on toxicity to insects are available. Bioaccumulation was considered to be of low concern. The risk to bees was assessed as low for the intended use on cotton, and the uses on tomato and aubergine in Northern European greenhouses. The risk to pollinators from the insect growth regulator mode of action, however, needs to be addressed further for greenhouse uses on tomato and aubergine in Southern Europe. The risk to soil non-target micro-organisms was not addressed due to the lack of valid studies. A new study was provided by the notifier and assessed by RMS in an addendum (December 2008), however this could not be considered in the peer review in view of the restrictions laid down in Commission Regulation (EC) No. 1095/2007. The risk to non-target arthropods, earthworms, soil non-target macro-organisms, non-target plants and biological methods for sewage treatment was assessed as low.

Key words: pyriproxyfen, peer review, risk assessment, pesticide, insecticide.

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BACKGROUND

Commission Regulation (EC) No 1490/2002[8] laying down the detailed rules for the implementation of the third stage of the work programme referred to in Article 8(2) of Council Directive 91/414/EEC and amending Regulation (EC) No 451/2000, as amended by Commission Regulation (EC) No 1095/2007 regulates for the European Food Safety Authority (EFSA) the procedure of evaluation of the Draft Assessment Report (DAR) provided by the designated rapporteur Member State.

Pyriproxyfen is one of the 79 substances of the third stage part A of the review programme covered by Commission Regulation (EC) No 1490/2002.

Pyriproxyfen was included in Annex I to Directive 91/414/EEC on 1 January 2009 pursuant to Article 11b of Commission Regulation (EC) No 1490/2002 (hereinafter referred to as 'the Regulation'). In accordance with Article 12a of the Regulation the EFSA is required to deliver by 31 December 2010 its view on the draft review report submitted by the Commission of the European Communities (hereinafter referred to as 'the Commission') in accordance with Article 12(1) of the Regulation. This review report has been established as a result of the initial evaluation provided by the designated rapporteur Member State in the Draft Assessment Report (DAR). The EFSA therefore organised a peer review of the DAR. The conclusions of the peer review are set out in this report.

In accordance with the provisions of Article 10(1) of the Regulation, the Netherlands submitted the DAR on pyriproxyfen (Netherlands, 2005), which was received by the EFSA on 24 November 2005. Following an administrative evaluation, the DAR was distributed for consultation in accordance with Article 11(2) of the Regulation on 21 July 2006 to the Member States and to the sole notifier Sumitomo Chemical Agro Europe S.A., as identified by the rapporteur Member State.

The comments received on the DAR were evaluated and addressed by the rapporteur Member State. Based on this evaluation, the EFSA identified and agreed with Member States during a written procedure in September – October 2007 on lacking information to be addressed by the notifier as well as issues for further detailed discussion at expert level.

Taking into account the requested information received from the notifier, a scientific discussion took place in expert meetings in January 2009. 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 during a written procedure with the Member States in March 2009.

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 Protection Products and their Residues (PPR).

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 A.

The documentation developed during the peer review was compiled as a peer review report (EFSA, 2009) comprising of the documents summarising and addressing the comments

[8] OJ L224, 21.08.2002, p.25, as amended by Regulation (EC) No 1095/2007 (OJ L246, 21.9.2007, p.19).

received on the initial evaluation provided in the rapporteur Member State's draft assessment report:

- the comments received,
- the resulting reporting table (revision 1-2; 4 January 2008),

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 (revision 2-1; 16 July 2009).

Given the importance of the draft assessment report including its addendum (compiled version of February 2009 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

Pyriproxyfen is the ISO common name for 4-phenoxyphenyl (*RS*)-2-(2-pyridyloxy)propyl ether (IUPAC).

Pyriproxyfen, belongs to the class of juvenile hormone mimics, other examples of this class are fenoxycarb and methoprene. The mode of action is suppression of embryogenesis, and inhibition of metamorphosis and reproduction. The representative formulated product for the evaluation was 'Pyriproxyfen 10 EC', an emulsifiable concentrate (EC). The evaluated physchem data showed that the formulation should be classified as R65 aspiration hazard.

The evaluated representative uses are as an insecticide on protected tomato and aubergine[9] and field grown cotton. Full details of the GAP can be found in the end points.

SPECIFIC CONCLUSIONS OF THE EVALUATION

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

The minimum purity of pyriproxyfen as manufactured should not be less than 970 g/kg, this is in line with the FAO specification 715/TC July 2006.

For the specification, clarification is necessary with respect to the proposed maximum content of two significant impurities. However, it should be noted that the specification was accepted by mammalian toxicology. The technical material contains a relevant impurity, toluene, its content in the technical material must not exceed 5 g/kg.

The content of pyriproxyfen in the representative formulation is 100 g/L (pure).

The assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the identity, physical, chemical and technical properties of pyriproxyfen or the respective formulation. However, the following data gaps were identified:

- QC data to support the specification unless the non-relevant impurities in question are removed from the specification.
- Biological activity of the isomers

[9] Also referred to in the DAR as egg plant

- Relative density
- Spectra IR, 1H-NMR and mass
- Water solubility
- Partition co-efficient
- Henry's law constant
- Oxidising properties of the formulation
- Details of the commercial packaging. If the packaging is different to that tested in the storage stability studies then further data may be required.

It should be noted that new studies have already been provided for biological activity of the isomers, relative density, spectra, water solubility, partition co-efficient and Henry's law constant and are evaluated in the addendum to Volume 3-B1-B5 (December 2008) from the Final Addendum to the DAR (Netherlands, 2009). However, in accordance with Regulation 1095/2007 they were not considered by the peer review and they remain as data gaps.

The main data regarding the identity of pyriproxyfen and its physical and chemical properties are given in appendix A.

Sufficient test methods and data relating to physical, chemical and technical properties are available. In addition, adequate analytical methods are available for the determination of pyriproxyfen in the technical material and in the representative formulation as well as for the determination of the respective impurities in the technical material.

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 where finalised, i.e. pyriproxyfen in food of plant origin (high water content and oily matrices) soil, water and air. It should be noted however that the residue definition for surface water is provisional.

Residues in food of plant origin and soil can be determined with a multi-method (the German S19 method has been validated). The LOQ for food and feed of plant origin and soil was 0.01 mg/kg. The method of analysis for water was GC-NPD with a LOQ of 0.01 µg/L the confirmatory method was by GC-MS. Air was analysed by GC-NPD with a LOQ of 1.0 µg/m^3 the confirmatory method was GC-MS.

An analytical method for food of animal origin is not required due to the fact that no residue definition is proposed (see 3.2). Methods for body fluids and tissues are not required as the active substance is not classified as toxic or very toxic.

2. Mammalian toxicity

Pyriproxyfen was discussed by the experts in mammalian toxicology in January 2009 (PRAPeR meeting 64, round 13), taking into account the addendum to Volume 3-B6 (December 2008) from the Final Addendum to the DAR (Netherlands, 2009).

Based on the available information in Volume 4 of the DAR, the toxicological batches were considered equivalent to the technical specification. The experts agreed that toluene is a toxicologically relevant impurity but its level in the technical specification is not of concern since it is covered by the level tested within the toxicological batches.

Since pyriproxyfen is produced as a racemic mixture of enantiomers, it was agreed that the same mixture was present in the batches used for the toxicological studies. No information was available on the toxicity of the individual isomers.

2.1. Absorption, distribution, excretion and metabolism (toxicokinetics)

The derivation of the oral absorption value was discussed by the experts, based on the available data and on further explanations in the addendum. It was agreed to base this value on data from bile-cannulated rats, including radioactivity in bile and urine (+ cage wash). The amounts of radiolabelled substance in tissues were not measured in these animals but were expected to be very low based on the results in non-cannulated animals. Consequently the agreed oral absorption value was 40%, and was considered as a worst-case estimate for risk assessment purposes.

The distribution of pyriproxyfen in the body after oral administration was limited. Only 0.1-0.3% of the administered dose was retained in tissues, with the highest concentrations in fat and liver and without evidence of accumulation. The excretion was fast, mainly via faeces (46-74% within 24h) and also via urine (3-9% within 24h). Pyriproxyfen was extensively metabolised, the main metabolic route being hydroxylation at the 4-position followed by a further hydroxylation step and conjugation.

2.2. Acute toxicity

Pyriproxyfen was a compound of low acute toxicity in all tested species (rats, mice and dogs); either by oral and dermal exposure, or by inhalation (oral LD_{50} >5000 mg/kg bw; dermal LD_{50} >2000 mg/kg bw; LC_{50} >1.3 mg/L, maximum attainable concentration). Pyriproxyfen did not show skin or eye irritating properties, and had no skin sensitizing properties in a maximisation test.

2.3. Short-term toxicity

The short-term oral toxicity of pyriproxyfen was investigated in rats (one 4-week study, one 13-week study and one 6-month study) and in dogs (one 4-week study, one 90-day study and two 52-week studies). In both species, the main target organ was the liver, as shown by changes in the biochemistry parameters, increases in liver weight, and histopathological alterations in the liver at high doses (682 mg/kg bw/day in rats, 300 mg/kg bw/day in dogs). Slight changes in haematological parameters were also observed in rats and dogs at lower dose levels (29 and 100 mg/kg bw/day). The relevant oral NOAEL in the rat was 24 mg/kg bw/day based on the 13-week and 6-month studies. The experts agreed on a relevant oral NOAEL in the dog of 10 mg/kg bw/day based on a consistent increase of the cholesterol level and a significant increase of the liver weight in males at the low dose level (30 mg/kg bw/day) in the first 52-week study, and no adverse effect at the high dose (10 mg/kg bw/day) in the second 52-week study.

Short term effects were also studied after dermal exposure (21-day, rat) or exposure by inhalation (28-day, rat). The relevant dermal NOAEL was 1000 mg/kg bw/day (highest dose tested). The experts agreed on a relevant NOAEC by inhalation of 482 mg/m³ (equivalent to 87 mg/kg bw/day) based on clinical effects and liver findings at 1000 mg/m³, as a conservative approach since the liver is the target organ.

2.4. Genotoxicity

Pyriproxyfen did not induce point mutations in bacterial cells (Ames test) both with and without metabolic activation. Negative results were also obtained during the *in vitro* chromosome aberration and gene mutation tests with Chinese hamster cells. In addition, pyriproxyfen was negative in an *in vitro* DNA repair study using human epithelioid cells. With regard to the *in vivo* testing, negative results were obtained in the mouse micronucleus test. Therefore, based on the available evidence, it was concluded that pyriproxyfen has no genotoxic potential.

2.5. Long-term toxicity and carcinogenicity

The chronic toxicity and carcinogenicity of pyriproxyfen was studied in rats (2-year study) and in mice (78-week study). The main target organ was the liver (rats and mice), but adverse effects were also observed in the kidneys and in the red blood cells (mice). The agreed NOAEL in rats was 27.2 mg/kg bw/day based on effects in clinical biochemistry and increased liver weight. The relevant NOAEL in mice was 16.4 mg/kg bw/day based on a reduced survival rate, increased liver weight, increased severity of systemic amyloidosis and histopathological changes in kidneys. None of the studies showed any evidence of a carcinogenic potential.

2.6. Reproductive and developmental toxicity

Investigations of the reproductive toxicity of pyriproxyfen were performed in a rat multigeneration study and in two teratogenicity studies (one with rats and the other with rabbits). Two additional rat studies with a modified design (not according to OECD guidelines) were also evaluated as acceptable in the DAR, and considered by the experts as confirming the results of the studies that were performed following the OECD guidelines (for reproductive and developmental effects).

The liver findings in the multigeneration study were discussed by the experts. The only adverse effect was increased liver weight, since no clinical chemistry and limited histopathological examinations are usually performed in a reproductive toxicity study. Based on this effect in the main target organ, and considering the evidence from other studies (short term and long term) which had NOAELs in the same range, the agreed parental NOAEL was 13.3 mg/kg bw/day. In the absence of effects on the reproductive parameters, the agreed NOAEL was 333.3 mg/kg bw/day. Based on a reduced body weight development in pups, the agreed offspring NOAEL was 66.7 mg/kg bw/day.

In the developmental toxicity studies, no teratogenic effect was observed in either species whereas developmental effects were noted in rats at maternal toxic doses (increased incidence of opening of foramen transversarium of the 7th cervical vertebra). Severe maternal toxicity, including mortalities, was observed at the high dose in both species, leading to an insufficient number of dams in the rabbit study to draw reliable conclusions for the highest dose group. Therefore the agreed developmental NOAELs were 100 mg/kg bw/day in rats and 300 mg/kg bw/day in rabbits; and the maternal NOAEL was 100 mg/kg bw/day for both species.

2.7. Neurotoxicity

No neurotoxicity studies were submitted or considered necessary since no indication of a neurotoxic effect of pyriproxyfen was shown in the available studies.

2.8. Further studies

No mechanistic studies with pyriproxyfen were provided, or considered necessary.

No toxicological studies with metabolites of pyriproxyfen were submitted in the dossier.

The relative toxicity of the plant metabolite PYPA[10] in comparison with pyriproxyfen was discussed by the experts (see also 3.1.1). PYPA was not detected in the rat metabolism studies. Based on the assumed metabolic pathway, the experts agreed that it was probably an intermediate in the whole degradation pathway, and that it would also be covered by the reference values of pyriproxyfen.

2.9. Medical data

During medical surveillance of plant workers (from 1995 to 2001), no clinical health problems were reported among workers handling pyriproxyfen. Similarly, no cases of toxicity or poisoning incidents have been reported.

2.10. Acceptable daily intake (ADI), acceptable operator exposure level (AOEL) and acute reference dose (ARfD)

Acceptable Daily Intake (**ADI**)

The dog was the most sensitive species. As proposed in the DAR, the agreed ADI was 0.1 mg/kg bw/day based on the 1-year dog study, with the use of a safety factor of 100.

Acute Reference Dose (**ARfD**)

Based on the toxicity profile of pyriproxyfen, the experts agreed that the derivation of an acute reference dose was not necessary.

Acceptable operator exposure level (**AOEL**)

Considering the exposure time for the worker (which might be longer than for operator), the experts agreed to use the 1-year dog study to derive the AOEL, as proposed in the DAR. Applying a correction for oral absorption (40%) and a safety factor of 100, the agreed AOEL was 0.04 mg/kg bw/day.

2.11. Dermal absorption

The results of a dermal absorption study *in vitro* with 'Pyriproxyfen 10 EC' were presented in the DAR. The study was performed with epidermal membranes from rats and humans. For this lipophilic substance, the experts agreed with the inclusion of all tape strips to estimate

[10] metabolite PYPA: (RS)-2-(2-pyridyloxy)propyl alcohol

the potentially absorbed dose. It was also noted that the exclusion of the first two tape strips would give a same value for the concentrate and a value negligibly lower for the spray dilution. Therefore the proposal from the DAR was accepted and the agreed dermal absorption values were 2.5% for the concentrate and 13% for the dilution.

2.12. Exposure to operators, workers and bystanders

The representative plant protection product 'Pyriproxyfen 10 EC' is an emulsifiable concentrate containing 100 g pyriproxyfen/L for use in field (cotton) and greenhouse (tomato and aubergine).

Revised calculations for the operator, bystander and worker exposure assessment were provided in the addendum to Vol.3 – B.6 (December 2008).

Operator

During the outdoor use, 'Pyriproxyfen 10 EC' is applied by mechanical downward spraying using a tractor-mounted, tractor-pulled and self-propelled ground sprayer. The exposure estimates were calculated using the UK POEM[11] (75th percentile) and the German model[12] (geometric mean). For the indoor application by manual up- and downward spraying, the Dutch model[13] (90th percentile) was used for the exposure estimates.

Estimated exposure presented as % of AOEL (0.04 mg/kg bw/day), according to calculations with the German and UK POEM model. The default for body weight of operator is 70 kg in the German model and 60 kg in the UK-POEM model.

[11] UK POEM: Scientific Subcommittee on Pesticides and British Agrochemicals Joint Medical Panel., Estimation of Exposure and Absorption of Pesticides by Spray Operators (UK MAFF, 1986) and the Predictive Operator Exposure Model (POEM) (UK MAFF, 1992)

[12] German model: Uniform Principles for Safeguarding the Health of Applicators of Plant Protection Products (Uniform Principles for Operator Protections); Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirschaft, Berlin-Dahlem, n° 277, 1992

[13] Dutch greenhouse model: Van Golstein Brouwers Y.G.C., Marquart J., Van Hemmen J.J. (1996) Assessment of occupational exposure to pesticides in agriculture. Part IV. Protocol for the use of generic exposure data. TNO Nutrition and Food Research Institute, The Netherlands. TNO Report V 96.120

Use	Model	Without PPE	With PPE*
Outdoor (cotton)	UK POEM	74	10
Outdoor (cotton)	German model	18	14
Indoor (tomato/aubergine, Northern Europe)	Dutch model	29	4
Indoor (tomato/aubergine, Southern Europe)	Dutch model	108	15

*PPE (personal protective equipment): for UK POEM: gloves during mixing/loading and application; for German model: gloves during mixing/loading only; for Dutch model: gloves and coverall during mixing/loading and application (no respiratory protective equipment).

Based on these results, the operator exposure estimates are below the AOEL without the use of personal protective equipment during outdoor application and indoor application in Northern Europe. However the indoor application in Southern Europe requires the use of personal protective equipment in order to reduce the exposure level below the AOEL.

Bystander

In greenhouses, no bystander exposure during application is expected since Good Agricultural Practice requires that bystanders are not present.

For the estimation of the bystander exposure during outdoor use, the draft values of the EUROPOEM II model[14] were used (90th percentile). The resulting systemic exposure represents <1% of the AOEL.

Worker

For the estimation of the worker exposure during re-entry activities (harvesting of cotton, cutting and sorting of tomato/aubergine), the draft values of the EUROPOEM II model were used. The default dislodgeable foliar residue of 30 mg a.s./m²/kg a.s./ha was used, as well as a transfer coefficient of 0.45 m²/hour. The resulting exposure estimates are below the AOEL even without the use of gloves (see figures in the table below).

[14] EUROPOEM II : van Hemmen J.J, Chester G., Hamey P., Kangas J., Kirknel E., Maasfeld W., Perkins J., Phillips J., Rosario C. (2002). Post-application exposure of workers to pesticides in agriculture. EUROPOEM II PROJECT FAIR3-CT96-1406. Draft Report of the Re-entry Working Group, December 2002

Estimated exposure presented as % of AOEL (0.04 mg/kg bw/day), according to calculations with EUROPOEM II. The default for body weight of operator is 70 kg.

Use	Without PPE	With PPE*
Outdoor (cotton)	28	3
Indoor (tomato/aubergine, Northern Europe)	11	1
Indoor (tomato/aubergine, Southern Europe)	42	4

*PPE (personal protective equipment): gloves.

EFSA notes: In the addendum of December 2008 consideration was also given to the number of applications. The worker exposure has been calculated after one application. It is possible that worker exposure is higher after two applications. However this cannot be quantified with the existing models. In this case, even the unrealistic worst-case assumption of 200% active substance on the crop would still result in exposure levels below the AOEL for the worker without the use of PPE.

3. Residues

The pyriproxyfen molecule contains an asymmetric carbon atom and can therefore exist as both (R)- and (S)-isomer. All residue studies were performed with the racemic mixture of both isomers and no stereo-specific determination was performed. Therefore the regulatory dossier provides no information on the behaviour of each individual pyriproxyfen enantiomer in crops and livestock. Therefore all residues reported as pyriproxyfen in this conclusion are for the sum of the 2 enantiomers. It is not known if either isomer is degraded more quickly than the other in the matrices studied.

3.1. Nature and magnitude of residues in plant

3.1.1. Primary crops

Studies on the metabolism of pyriproxyfen were submitted in apple, in tomato and in cotton with radio labelled compound ([U-phenoxyphenyl-^{14}C]- and [2,6 pyridyl-^{14}C] pyriproxyfen).

Only the results for tomato and cotton were considered to evaluate the notified representative uses of pyriproxyfen on tomato, aubergine and cotton.

In both the tomato study and the cotton study, the number of treatments, dose and PHI interval deviated from the defined critical GAP towards a higher application rate or number of applications, respectively (*ca* 2N tomato Southern Europe, *ca* 7N tomato Northern Europe and *ca* 4 N cotton Southern Europe), but to a longer PHI of 7 instead of 3 days (tomato). The fact that pyriproxyfen was metabolised rather slowly allows the establishment of the metabolism pathway, despite the above-mentioned deviations from the cGAP.

The studies indicated pyriproxyfen is only partly metabolised in tomato, but more extensively in cotton seed. The major pathways in the metabolisation and degradation of pyriproxyfen in

crops involved hydroxylation steps to form hydroxy analogues of pyriproxyfen such as 4'-OH-pyr[15], cleavage of the ether linkages to form amongst others POP[16], 2-OH-PY[17] and PYPA, followed by oxidation (PYPAC[18]) and/or conjugation and/or incorporation into natural plant constituents.

The major component identified in tomato was pyriproxyfen (50-68% TRR). The metabolite PYPA (free and conjugated) was present at about 11% TRR. All other compounds were present as minor metabolites, free and/or conjugated, with 4'-OH-pyr (6% TRR) and PYPAC (8% TRR) being the most important ones among these minor metabolites.

In cotton seed no major residue was detected. Pyriproxyfen represented ≤4% of TRR. Other minor components identified were 4'-OH-pyr (<1% TRR), PYPAC (8% TRR), PYPAC-Asp[19] (5% TRR) and free and conjugated and PYPA (4% TRR). A significant part of the radioactivity in cotton seed (71-81% TRR) was shown to be incorporated into fatty acids, protein, cellulose/hemicellulose and lignin.

In cotton gin trash, pyriproxyfen was by far the major component identified (36-43% TRR). All other components of the residue were below 10% of the TRR. 4'-OH-pyr (7% TRR) and DPH-pyr[20] (7% TRR), both free and conjugated, were the most important minor metabolites in cotton gin trash. Incorporation of radioactivity in natural components, mainly protein and lignin, was observed (12-17% TRR).

There was a concern on the toxicological relevance of the metabolite PYPA because this metabolite was not recovered in the rat metabolism. The meeting on toxicology (PRAPeR 64) agreed that PYPA, based on the assumed metabolic pathway, is likely to be an intermediate in the rat as well (it occurs in the goat and in the hen) and that it is covered by the toxicological reference values of pyriproxyfen. Based on this information the experts in residues agreed that this metabolite should not be considered in the plant residue definition because of the low level of PYPA recovered in the studied crops when compared to the level of pyriproxyfen.

The residue definition for monitoring and risk assessment in terms of the notified uses in the fruit and oilseed crop category is therefore proposed as pyriproxyfen alone.

Supervised residue trials were conducted in tomato and cotton seed. All trial results are supported by validated analytical methods and sufficient storage stability data.

In total, 8 residue trials in greenhouse tomato (of which two in cherry tomato) in Southern Europe were submitted covering several growing periods (spring 1999 and 2000, autumn 1999 and 2000). All studies were performed according to the cGAP. Four of the eight residue trials were residue decline studies. The residue trials are also applicable to address residues in tomato grown in greenhouses in Northern Europe. According to current guidance, the data can moreover be used to extrapolate to aubergine.

On cotton, only 2 residue trials according to cGAP criteria performed in Southern Europe but only in one growing season (residues below 0.01 mg/kg) were submitted. It was noted that pyriproxyfen is a fat soluble compound and that occasional findings of residues in seeds might have been expected. The experts discussed whether further data should be required to

[15] 4'-OH-PYR: 4-(4'-hydroxyphenoxyphenyl) (RS)-2-(2-pryidyloxy)propyl ether
[16] POP: 4-phenoxyphenol
[17] 2-OH-PY: 2-hydroxypyridin
[18] PYPAC: (RS)-2-(2-pyridyloxy)propionic acid
[19] PYPAC-Asp: N-[(RS)-2-(2-pyridyloxy)propionyl]-(S)-aspartic acid
[20] DPH-pyr: 4-hydroxyphenyl (RS)-2-(2-pyridyloxy)propyl ether

confirm that no residues above the LOQ will occur in seeds at harvest. The experts considered that, as from the latest growth stage of application defined by the GAP, there should not be direct contact of pyriproxyfen with the seeds. Moreover, metabolism data (2N study) show that penetration of residues in the bolls is not significant and that residues of pyriproxyfen in seeds were <0.01 mg/kg when twice the notified dose is applied.

Altogether, the meeting of experts agreed that it was sufficiently demonstrated that no significant residues (at or above 0.01 mg/kg) will occur and that no further trials in cotton seed are necessary. However, the meeting noted that although in food items (seeds) no residues occurred, residues might occur in the feed items (e.g. gin trash), triggering further residue trials for livestock dietary risk assessment purposes, and in future for MRL setting purposes for feed items. At present, parts of the cotton plant other than seeds seem not to be a relevant feed item in Europe. If animal feeding practices were to change, additional residue trials in cotton would be required.

According to criteria set out in current guidance an investigation of residues in processed commodities was not triggered for the notified uses. However, in a hydrolysis study with conditions simulating pasteurisation, baking/brewing/boiling and sterilisation pyriproxyfen was found to be stable as no significant degradation products were identified.

The level of residues in processed products was determined in processing studies on tomato and cotton seed. Residues decreased in tomato juice, canned tomato, pureed tomato and ketchup processed from peeled tomatoes. The majority of residues was recovered in the tomato peel. In tomatoes processed without peeling a slight concentration of residues was noted in pureed tomatoes.

Apparently in crude and refined cotton oil as well as in the pressed cotton cake residues decreased upon processing.

3.1.2. Succeeding and rotational crops

A confined rotational crop study with radio-labelled pyriproxyfen ([U-phenoxyphenyl-^{14}C]- and [2,6 pyridyl-^{14}C] label) was submitted including the relevant crop categories, i.e. cereals, leafy and root crops. The crops were grown in a greenhouse after treatment of the bare soil at a 0.9-fold rate, compared to the highest application rate notified.

Total residues were ≤0.007 mg eq/kg in lettuce and radish root and ≤0.081 mg eq/kg in wheat grain. Residue levels in feed items (radish leaf 0.011 mg eq/kg, wheat forage 0.011 mg eq/kg, straw 0.059 mg eq/kg and chaff 0.082 mg eq/kg) were all below 0.1 mg/kg.

Upon further investigation, the majority (89%) of the TRR in grain was shown to be incorporated into natural plant constituents. The extractable radioactivity of wheat straw and chaff contained up to 5 unidentified fractions, however all individually less than 10% TRR and not greater than 0.01 mg eq/kg. Due to the low levels residues in lettuce, radish and wheat forage were not further investigated.

On the basis of the DT90 for pyriproxyfen (max 54 days) rotational crop studies were not required. However, the meeting of experts noted that the metabolite 4'-OH-PYR had a higher persistence in soil (max DT90 157 days), and hence might be taken up by following crops.

The soil dissipation study demonstrated that the highest concentration of this metabolite occurred in the soil up to 14 days after application. In the rotational crop study, residues of individual compounds were not recovered in significant amounts in the rotated crops planted at a 30 day plant back interval. It is expected from soil dissipation data that the highest

concentration of this metabolite had been present in soil before or during the studied 30-day plant back interval. In crops planted at this interval no single residue fraction exceeded 0.01 mg/kg. Therefore it is considered unlikely that significant residues (>0.01 mg/kg) of this metabolite would be present in crops at plant back intervals longer than 30 days. Hence the experts agreed that no further data on rotational crops would be necessary.

3.2. Nature and magnitude of residues in livestock

Residues in livestock feed are not expected to occur at significant levels (<0.1 mg/kg in animal feed) as the only potential feed item according to current European guidance is cotton seed meal (residues <0.01 mg/kg). The more recent OECD Guidance Document (OECD, 2006) includes also cotton gin trash as a feed item that might locally be used in beef cattle diet. This feeding practice seems not to be relevant in Europe. However, even if cotton gin trash were used the dietary livestock intake would not be significant (calculation in the addendum to Volume 3-B7 (December 2008) from the Final Addendum to the DAR (Netherlands, 2009).

Nevertheless, studies on the metabolism of pyriproxyfen in livestock were submitted (two in goat and two in hen) and evaluated in the DAR for future reference.

It was concluded that in terms of the representative uses residues of pyriproxyfen are not likely to occur in animal products. At the moment, a residue definition for animal products and MRLs are not necessary, nor are further data (feeding studies) required.

3.3. Consumer risk assessment

An estimate of the theoretical maximum daily intake (TMDI) of pyriproxyfen by consumers with the established MRLs resulted in residue intakes of 0.34% of the ADI of 0.1 mg/kg bw/day for adults when using the FAO/WHO GEMS Food European diet.

In the addendum to Volume 3-B7 (February 2009) from the Final Addendum to the DAR (Netherlands, 2009) the consumer risk was assessed according to EFSA PRIMo rev.2, on the basis of the proposed MRLs of 0.3 mg/kg for tomato and aubergine, and of 0.01* mg/kg for cotton seed as well as residues assumed at default level (MRLs at LOQ 0.01* mg/kg) for all other plant commodities. The five highest results were obtained for the WHO Cluster diet B (1.5% ADI), the French toddler and German child (0.9% ADI, respectively) and the UK Toddler and NL child (0.8% ADI, respectively).

An ARfD was considered not necessary based on the low toxicity profile of pyriproxyfen. Therefore, an acute consumer risk assessment is not required.

As pyriproxyfen is a mixture of isomers information was required to address whether one of the two isomers (R)-pyriproxyfen or (S)-pyriproxyfen might be preferentially metabolised by crops, resulting in one of the isomers being the more pertinent or even the main residue, since this may have an impact on the consumer risk assessment. Based on the literature data, one isomer is more biologically active than the other. No information was however made available on the toxicity of the individual isomers or of different ratios of these isomers. Neither was data or information available on the ratio of the individual isomers in the residues in food commodities, since no stereo-specific methods of analysis were used in the residue trials and studies. To conclusively address consumer exposure and consumer risk such data would be necessary.

However, the experts agreed that under the specific conditions of use as assessed in the DAR residue intakes by consumers will be very low when compared to the acceptable daily intake for pyriproxyfen as used in the available toxicological studies. Furthermore, the experts considered that even if these residues didn't consist of the isomer ratio tested in the toxicological studies but of a different, more critical isomer ratio with regard to human toxicology, the margin of safety would be sufficiently large to exclude a dietary intake concern for consumers.

It is noted that for uses other than those assessed during the peer review procedure the issue will have to be reconsidered.

3.4. Proposed MRLs

All submitted trials in tomato were included for the MRL proposal for tomato. By extrapolation the data were also used to propose an MRL for aubergine.

For cotton seed the MRL was proposed at the validated LOQ of the analytical method.

Proposed MRLs for pyriproxyfen:

Tomato	0.3 mg/kg
Aubergine	0.3 mg/kg
Cotton seed	0.01* mg/kg

4. Environmental fate and behaviour

Pyriproxyfen was discussed at the PRAPeR experts' meeting for environmental fate and behaviour, PRAPeR 62 in January 2009. It should also be noted that the methods of analysis used in all the fate and behaviour studies were not stereoselective. Therefore the regulatory dossier provides no information on the behaviour of each individual pyriproxyfen enantiomer in the environment. Therefore all residues reported as pyriproxyfen in this conclusion are for the sum of the 2 enantiomers. It is not known if either isomer is degraded more quickly than the other in the environmental matrices studied.

4.1. Fate and behaviour in soil

4.1.1. Route of degradation in soil

Soil experiments (7 different soils) were carried out under aerobic conditions in the laboratory (25°C and 75% field capacity (FC) or 20°C 45% maximum water holding capacity (MWHC) in the dark). The formation of residues not extracted by methanol was a sink for the applied phenoxyphenyl ring-^{14}C-radiolabel or pyridyl-2,6-^{14}C-radiolabel (51-58 % and 30-49 % of the applied radiolabels (AR) respectively, after 90-122 days). Mineralisation to carbon dioxide of these radiolabels accounted for 11-42.5% and 24-61 % AR respectively after 90-94 days. There were no major (>10 % AR) extractable breakdown products present at any sampling time. Two transformation products 4'-OH-pyr and PYPAC exceeded 5% AR at 2 sampling events, and therefore trigger assessment for groundwater exposure. These were present at maxima of 0.9-6.3% AR and 1.0-8.6% AR respectively, both metabolites having these maxima occur between 1 and 14 days.

Data on anaerobic degradation in soil were not available. However these data are not necessary to complete an assessment for the applied for representative uses (i.e. glasshouse fruiting vegetables and cotton) as it is not expected that anaerobic soil conditions will occur in these production systems. In a laboratory soil photolysis study, no novel photodegradation products were identified. Though the degradation of parent pyriproxyfen was faster in irradiated samples than in the dark controls in the single soil studied, the irradiated DT_{50} values estimated (ca. 30 days, mean of 2 radiolabels equated to 43°N) is longer than in the optimised dark laboratory incubations in the other 7 soils.

4.1.2. Persistence of the active substance and their metabolites, degradation or reaction products

The rate of degradation of pyriproxyfen was estimated from the results of the studies described in 4.1.1 above. DT_{50} were: 8.3-17 days (single first-order non-linear regression, 25°C 75% FC, 3 different soils) or 2.8-6.1 days (single first-order non-linear regression, 20°C 45% MWHC, 4 different soils). After normalisation to FOCUS reference conditions[21] (20°C and -10kPa soil moisture content) this range of single first-order DT_{50} is 2.8-20.4 days (geometric mean that is appropriate for use in FOCUS modelling 6.7 days).

Single first-order linear regression decline DT_{50} (that represent the sum of a formation rate constant from the precursor and degradation rate constant of a transformation product) were estimated from the maximum measured occurrence for the metabolites 4'-OH-pyr and PYPAC in the available laboratory incubations where pyriproxyfen was dosed. For 4'-OH-pyr these DT_{50} values were calculated to be: 47 days (25°C 75% FC, in one soil) or 24-30 days (20°C 45% MWHC, 3 different soils). After normalisation to FOCUS reference conditions (20°C and -10kPa soil moisture content) this range of single first-order DT_{50} is 24-57 days (geometric mean that is appropriate for use in FOCUS modelling 32.8 days). For PYPAC these DT_{50} values were calculated to be: 14 and 25 days (25°C 75% FC, in 2 different soils) or 0.4 days (20°C 45% MWHC, in one soil). After normalisation to FOCUS reference conditions (20°C and -10kPa soil moisture content) this range of single first-order DT_{50} is 0.4-29 days (geometric mean that is appropriate for use in FOCUS modelling 5.9 days).

Though not formally triggered field soil dissipation studies (bare soil) were provided from 3 sites in the USA (Mississippi, Washington and New York) where applications were made between May and August. Using the residue levels of pyriproxyfen, determined over the top 7.5 or 30cm, non-linear regression single first-order DT_{50} for dissipation were 3.5-5.9 days. 4'-OH-pyr and PYPAC were analysed for but the concentrations measured (at around the limit of quantification of 0.02 mg/kg, when detected) and sporadic detection meant that it was impossible to estimate DT values for these metabolites.

The longest available laboratory pyriproxyfen, single first-order soil DT_{50} of 25 days calculated at a temperature of 20°C (from the 25°C DT_{50} of 17 days[22], but not normalised for soil moisture) was agreed by the experts from the member states as appropriate for use in PEC soil calculations.

[21] Using section 2.4.2 of the generic guidance for FOCUS groundwater scenarios, version 1.1 dated April 2002, utilising a Q10 of 2.2 and Walker equation coefficient of 0.7.
[22] utilising a Q10 of 2.2.

4.1.3. Mobility in soil of the active substance and their metabolites, degradation or reaction products

The adsorption / desorption of pyriproxyfen was investigated in 4 soils in satisfactory batch adsorption experiments. Calculated adsorption K_{Foc} values varied from 11000 to 34200 mL/g, (mean 21175 mL/g) (1/n 1.1 – 1.2, mean 1.15). There was no evidence of a correlation of adsorption with pH.

The adsorption / desorption of 4'-OH-pyr was investigated in three soils in satisfactory guideline batch adsorptions experiments. Calculated adsorption K_{Foc} values were 921-3811 mL/g (mean 2598 mL/g) (1/n 0.77 – 1.0, mean 0.87). There was no evidence of a correlation of adsorption with pH.

The adsorption / desorption of PYPAC was investigated in three soils in satisfactory guideline batch adsorptions experiments. Calculated adsorption K_{Foc} values were 9-32 mL/g (mean 20.7 mL/g) (1/n 1.0 – 1.2, mean 1.07). There was no evidence of a correlation of adsorption with pH.

The adsorption K_{doc} of DPH-pyr (a major water metabolite in aerobic laboratory sediment water system incubations) was estimated as 9620 mL/g using the Quantitative structure activity relationship (QSAR) software PCKOCWIN[23]. However this compound (a phenol) might be expected to exhibit pH dependent adsorption. The compound will be ionised in sediment water systems that will be predominantly neutral or alkaline. In the available sediment water studies this metabolite was major in the water phase which is not consistent with this very high QSAR value that represents the not ionised form. This QSAR K_{doc} value will considerably overestimate the partitioning potential of DPH-pyr to sediment when using FOCUS surface water STEP 1 and 2 exposure estimation tools. In the absence of any other K_{oc} estimation, FOCUS surface water STEP 1 and 2 calculations should utilise a default K_{doc} of 10 mL/g as input to generate a surface water exposure estimate. For the calculation of PEC sediment only, would it be appropriate to retain a high K_{doc} value such as 9620 mL/g.

4.2. Fate and behaviour in water

4.2.1. Surface water and sediment

Pyriproxyfen was stable under sterile hydrolysis conditions at 50°C at pH 4, 7 and 9. In a laboratory study where the aqueous photolysis of pyriproxyfen was investigated under sterile conditions, a rate of degradation (single first-order DT_{50}) of 11.5 days equated to summer sunlight at 43°N was determined. Pyriproxyfen degraded to PYPA which accounted for 70% AR after 14 days in this test system. This rate of photolytic degradation is slower than was observed in the biologically active water sediment study (whole system values 5.4-7.8 days, single first-order) and significantly slower than the rate of partition from water to sediment (estimated at 1.4-1.7 days, single first-order), indicating that in non-sterile natural systems this novel breakdown product PYPA would not be expected to be formed in significant amounts.

A ready biodegradability test (comparable protocol to that defined in OECD 301C) indicated that pyriproxyfen is 'not readily biodegradable' using the criteria defined by this test.

In water-sediment studies (2 systems studied at 20°C in the laboratory) pyriproxyfen partitioned to the sediment where it degraded (non-linear regression single first-order whole system DT_{50} 5.4-7.8 days). The metabolite 4-OH-pyr (max. 9.2-14.8 % AR at 14-50 days after

[23] Version 1.63 (Syracuse Research Corporation, 1996).

treatment, in sediment) only accounted for a maximum of 4.8% AR in the water phase and was estimated to degrade with a non-linear regression single first-order DT_{50} of 0.8-1.7 days (whole system value in an experiment where this metabolite was dosed to the system). DPH-pyr accounted for a maximum of 11.8 % AR at 2 days in the water phase but was in sediment extracts at a maximum of 4.3 % AR. PYPAC accounted for a maximum of 23.6 % AR at 100 days in the water phase but was in sediment extracts at a maxima of 7.6 % AR. It was estimated to degrade with a non-linear regression single first-order DT_{50} of 12 to 63 days (whole system value in an experiment where this metabolite was dosed to the system). The terminal metabolite, CO_2, accounted for 25-52 % of the phenoxyphenyl ring-^{14}C-radiolabel or 11-36 % of the pyridyl-2,6-^{14}C-radiolabel by 100 days. Residues not extracted from sediment by methanol water followed by acetone acetic acid were a significant sink representing 31-51% AR at study end (100 days). The experts agreed that for pyriproxyfen water and sediment a DT_{50} of 6.5 days (a geomean whole system value) was acceptable for use as FOCUSsw scenario calculation input.

FOCUS surface water modelling was evaluated up to step 3 for pyriproxyfen for the outdoor use on cotton and step 2 for pyriproxyfen under protection and for the metabolites 4'-OH-pyr, DPH-pyr and PYPAC (both outdoor and protected uses) The peer review agreed these PEC surface water and sediment values as presented in Appendix A to this conclusion (note: these values reflect those in the DAR for 4'-OH-pyr and PYPAC but differ for DPH-pyr as in Appendix A a different K_{doc} value was utilised (see section 4.1.3)).

4.2.2. Potential for ground water contamination of the active substance, their metabolites, degradation or reaction products

The applied for representative use of a summer application to cotton was simulated using FOCUS PEARL 1.1.1 and the following input parameters: pyriproxyfen single first order DT_{50} 8.6 days, K_{Foc} 21175 mL/g, 1/n=1.15; 4'-OH-pyr single first-order DT_{50} 34.8 days, K_{Foc} 2598 mL/g, 1/n=0.87 and PYPAC single first order DT_{50} 15.7 days, K_{Foc} 20.7 mL/g, 1/n=1.1. The two metabolites were modelled as if they were an active substance being applied at the soil surface. Application rates for the metabolites were calculated adjusting that of the parent active substance accounting for the observed maxima in the available soil incubations where the active substance had been dosed. This approach was accepted by the peer review in this case where the active substance is degraded relatively rapidly, is strongly adsorbed and the metabolite DT_{50} used represent an observed decline from the maximum observed formation in the available studies. It was noted that this approach would not be appropriate for many other substances as this combination criteria will not be respected in many assessments of other substances.

Parent pyriproxyfen, 4'-OH-pyr and PYPAC were calculated to be present in leachate leaving the top 1m soil layer at 80th percentile annual average concentrations of <0.001µg/L at the Sevilla and Thiva FOCUS groundwater scenarios that are parameterised for the cotton crop.

In the addendum to Volume 3-B8 (December 2008) from the Final Addendum to the DAR (Netherlands, 2009), additional FOCUS groundwater scenario simulations were provided to provide a groundwater exposure assessment, designed to encompass the applied for intended uses under protection on the fruiting vegetables tomato and aubergine. The experts from the member states discussed the applicability of these 'hybrid simulations' that combined the GAP requested for protected uses (tomato and aubergine) with the scenario definitions prescribed by FOCUS groundwater guidance for outdoor use on tomato. The experts agreed that this approach was expected to be conservative as simulations representing outdoor

conditions will result in more groundwater recharge of both solute and water than would be expected from indoor use when good irrigation practice is followed, at the very least for the standard Piacenza FOCUS groundwater scenario (outdoor conditions). It was noted that this groundwater assessment is based on the assumption that the use of the product is on only one crop per year and there is the possibility that this may not always be the case in all intensive protected production situations. Therefore, regarding the potential for groundwater exposure covered by this conclusion, only applications to 1 crop per year (i.e. up to 2 applications per calendar year) have been assessed for the protected uses on tomato and aubergine. This groundwater assessment used the same substance properties and approach to simulations for the metabolites that are outlined for cotton above.

Parent pyriproxyfen and 4'-OH-pyr were calculated to be present in leachate leaving the top 1m soil layer at 80th percentile annual average concentrations of <0.001µg/L at the Chateaudun, Piacenza, Porto, Sevilla and Thiva FOCUS groundwater scenarios that were utilised as parameterised for the outdoor tomato crop. These concentrations for PYPAC were 0.001 to 0.027µg/L.

4.3. Fate and behaviour in air

The vapour pressure of pyriproxyfen (<$1.33x10^{-5}$ Pa at 22.8°C) means that pyriproxyfen could be classified using Table 2.7-1 of the FOCUS air guidance (FOCUS, 2008) as exhibiting low volatility or being non-volatile from both soil and plant surfaces, indicating that significant losses due to volatilisation would not be expected. Calculations using the method of Atkinson for indirect photo-oxidation in the atmosphere through reaction with hydroxyl radicals resulted in an atmospheric half life estimated at 6 hours (assuming an atmospheric hydroxyl radical concentration of $6x10^5$ radicals cm^{-3}) indicating that the small proportion of applied pyriproxyfen that will reach the atmosphere (for example by forming aerosols at the time of application) would be unlikely to be subject to long range atmospheric transport.

5. Ecotoxicology

Pyriproxyfen was discussed in the meeting of ecotoxicology experts (PRAPeR 63) in January 2009, on the basis of the DAR and the addendum to Volume 3-B9 (December 2008) from the Final Addendum to the DAR (Netherlands, 2009). After the experts' meeting the RMS provided a further addendum to Volume 3-B9 (February 2009) from the Final Addendum to the DAR (Netherlands, 2009).

Pyriproxyfen is the active substance in the formulated product 'Pyriproxyfen 10 EC' (100 g/L), also referred to as 'Pyriproxyfen 100 g/L', 'Pyriproxyfen 10% EC', 'Pyriproxyfen 0.83 EC' and 'S-71639 10 EC', containing 10-11.5% Pyriproxyfen, or 98.0-100 g pyriproxyfen/L. The representative evaluated uses of pyriproxyfen were as an insecticide with foliar application in tomato and aubergine grown in glasshouses (1-2 applications at 10 days interval at 0.02-0.03 kg a.s./ha in Northern Europe and 1-2 applications at 10 days interval at 0.05-0.1125 kg a.s./ha in Southern Europe) and with foliar application in cotton in Southern Europe (single application of 0.075 kg a.s./ha).

Pyriproxyfen consists of two enantiomers and it is not known if there is any change in the ratio of these during degradation. Any change in the ratio would not necessarily be covered by the ecotoxicological endpoints of studies dosed with racemate. EFSA noted while drafting the conclusion that potentially the ecotoxicological risk assessment could underestimate the

risk by a factor of 2 (assuming the residue was only 1 isomer and all the toxicity came from this isomer).

The risk assessment was conducted according to the following guidance documents: Risk Assessment for Birds and Mammals (European Commission, 2002a); Aquatic Ecotoxicology (European Commission, 2002b); Terrestrial Ecotoxicology (European Commission, 2002c); Risk Assessment for non-target arthropods (SETAC, 2000).

5.1. Risk to terrestrial vertebrates

The first tier risk assessment to terrestrial vertebrates was assessed for generic species in a leafy crop scenario. For the glasshouse use only exposure to pyriproxyfen via consumption of contaminated surface water and secondary poisoning via consumption of fish from contaminated waters were considered since wild birds and mammals were not considered to have access to glasshouses.

Birds

The risk to herbivorous birds in cotton was considered to be low based on first-tier TERa of >384, TERst of >379 and TERlt of 58. The risk to insectivorous birds in cotton was also considered to be low since first tier TER values were clearly above the Annex VI trigger. TERa was >470, TERst was > 382 and TERlt was 31. The risk assessment for intake of contaminated drinking water was based on both PEC surface water (in DAR) and on concentration in leaf axils and puddles (Addendum, December 2008). TER values indicated a low risk from consumption of contaminated drinking water.

Mammals

The risk to herbivorous mammals in cotton was considered to be low based on first-tier TERa values of >2763 and TERlt of 29.9. The risk assessment for intake of contaminated drinking water was based on both PEC surface water (in DAR) and on concentration in leaf axils and puddles (Addendum, December 2008). TER values indicated a low risk from consumption of contaminated drinking water.

Metabolites

4'-OH-pyr was the only major (10%) metabolite detected in plants. This metabolite was also detected in hen, rat, mouse and goat in feeding studies. Toxicity values for birds were calculated based on the exposure level from the feeding studies and the exposure estimated from residues in plant material (apple pomace). For mammals the risk was considered to have been covered by the studies with the parent active substance since levels of 54.4 % of applied radioactivity were detected as the metabolite. The resulting TER values indicate a low risk for both birds and mammals. A risk assessment for minor plant metabolites (DPH-pyr, POP, POPA[24], PYPA, PYPAC) was conducted by the RMS based on maximum residue levels. For the metabolite detected in highest concentration, the toxicity would have to be 272 times more toxic to birds and 141 times more toxic to mammals than pyriproxyfen in order to result in a TER value below the Annex VI trigger. This was considered unlikely and the risk of the metabolites was considered to be low.

Secondary poisoning

The risk to earthworm- and fish-eating birds and mammals from secondary poisoning was considered to be low since the TER values were well above the Annex VI trigger.

[24] POPA: (RS)-2-hydroxypropylphenoxyphenyl ether

In summary, the risk was assessed as low for birds and mammals for all intended uses.

5.2. Risk to aquatic organisms

Pyriproxyfen was proposed to be classified as very toxic to aquatic organisms (R50) based on LC/EC_{50} values of >0.27, 0.40 and 0.094 mg a.s./L obtained for fish, daphnids and algae, respectively. The NOEC for reproduction was determined as 0.015 µg/L for *Daphnia magna* in a laboratory study, while the NOAEC from an available microcosm study was determined to 5.0 µg/L, based on class 2 effects and no assessment factor. It was noted in the expert meeting that insects were missing in the microcosm study, and a data gap was agreed to address the risk to aquatic insects, given the fact that it is an insect growth regulator. The formulation 'S-71639 10EC' has an acute toxicity in the same order of magnitude as expected from the content of technical pyriproxyfen but since the LC/EC_{50} values were somewhat lower these were used in the acute risk assessment. Since pyriproxyfen was not readily biodegradable it could be classified as R53 (May cause long term adverse effects in the aquatic environment).

Cotton

The first-tier acute risk from exposure to pyriproxyfen from the use in cotton was estimated by comparing the PEC_{sw} obtained by FOCUS Step 1 calculations with the EC/LC_{50} for different organisms. All acute TER values were well above the relevant Annex VI trigger indicating a low risk (TER_a= 142 for fish, 123 for invertebrates, 48 for algae and >117 for aquatic plants). The long-term TER value for *Chironimus riparius* was 14, and thus above the trigger when calculated with PEC_{sw} from FOCUS Step 2. For fish the TER_{lt} was 11 based on PEC_{sw} values from FOCUS Step 3, and hence the trigger was met. The chronic TER for *Daphnia magna* was 0.04 at FOCUS Step 3, which is far below the trigger and thus indicated a high risk to aquatic organisms. In the DAR the assessment was refined by using the NOAEC of 5 µg/L from the microcosm study. It was, however, agreed by Member State experts that the risk to aquatic invertebrates needs to be further addressed, as insects were not covered by the available microcosm study. EFSA noted (after the peer review) that although the risk to sediment-dwelling insects was addressed by the *C. riparius* study, this study could not be considered to cover effects on all other insects, given the mode of action (insect growth regulator). Member State experts agreed that an assessment factor should be considered when data on toxicity to insects are available, taking into account relative toxicity to insects and possible interactions between species.

Tomato and aubergine in glasshouses

The risk to aquatic organisms from the use on tomato and aubergine in glasshouses was calculated by comparing the relevant toxicity endpoints with PEC_{sw} calculated with FOCUS Step 2 but assuming 0.1% drift instead of the default value. All acute TER values were well above the respective Annex VI trigger. Also TER_{lt} for fish (TER=113) and *C. riparius* (TER=262) were above the Annex VI trigger, while the TER for *D. magna* was 0.39 indicating a high risk. As for the use in cotton, the assessment for aquatic invertebrates needed to be addressed further in a higher tier risk assessment also covering insects (see above).

Risk to sediment-dwelling organisms

Pyriproxyfen partitions to sediment. However, the risk to sediment dwelling organisms was considered to be low based on TER values for *C. riparius* that met the Annex VI trigger (see above). After the peer review EFSA noted that the TER calculation for *C. riparius* was based

only on water concentration (TER based on sediment concentration was not calculated). The assessment was however considered sufficient to address the risk to sediment dwellers, given the single application use in cotton.

Metabolites

Acute toxicity studies with the metabolite PYPAC (major metabolite in soil and water) show that this metabolite is clearly less toxic to aquatic organisms than pyriproxyfen and is therefore considered as not ecotoxicologically relevant. No studies were available with DPH-pyr, a metabolite that was detected >10% in the water phase of water/sediment studies. It was however likely that this metabolite would have been present in the microcosm study and the risk was therefore considered to be covered by the assessment for pyriproxyfen. EFSA, however, notes that the assessment of pyriproxyfen did not cover effects on aquatic insects, and therefore the risk to insects from DPH-pyr would also need to be addressed further (i.e. a data gap). The metabolite 4'-OH-pyr was detected >10% in the sediment of water/sediment studies at day 14 and also at day 30 in one study. This metabolite was however detected in the sediment of the *Chironimus* study using pyriproxyfen, and furthermore showed lower acute toxicity towards *Daphnia* compared to pyriproxyfen. The risk to sediment-dwelling organisms from exposure to 4'-OH-pyr was therefore considered to be covered by the assessment for pyriproxyfen.

Bioaccumulation

The BCF in whole fish for pyriproxyfen was determined as 660 and 501 for the pyridinyl and phenoxyphenyl labelled substance, respectively. Of the pyridinyl-labelled substance 10.4% was detected as residues in the whole fish after 14 days of depuration. The DT_{90} was determined to be approximately 100 days in sediment and the risk from bioaccumulation therefore needs to be considered. The risk assessment for fish was based on an early life stage study and the Annex VI trigger was met indicating a low long-term risk to fish. Furthermore, the risk to fish-eating birds and mammals was considered to be low. Therefore, bioaccumulation was considered to be of low concern.

Overall the risk to aquatic organisms could not be addressed based on the submitted data, as the available higher tier microcosm study did not cover aquatic insects. A data gap remains for the notifier to include insects in the aquatic risk assessment.

5.3. Risk to bees

Acute oral and contact toxicity to bees was tested with the formulated product 'Pyriproxyfen 10 EC'. Toxicity to adult bees was low and hazard quotients were calculated to be less than 1.5. Mortality of adults and juvenile stages, overall colony performance, and survival and development of eggs and larvae to adult emergence were studied in a 60-day field study with application of 75 g a.s./ha, to examine the potential effects of an insect growth regulator. No differences compared to an untreated control were detected. Therefore, the risk to bee brood from the use of pyriproxyfen in cotton (1 application of 75 g a.s./ha) and on tomato and aubergine in Northern Europe (1-2 applications of 30 g a.s./ha) was considered to be low. However, for the use in tomato and aubergine in Southern Europe (1-2 applications of 112.5 g a.s./ha) the risk to bee brood needed to be further addressed. Member State experts agreed that further studies would be necessary to address the risk from the uses on tomato and aubergine in greenhouses in Southern Europe. Member State experts supported the recommendation from the RMS to include an appropriate safety phrase on the label.

The risk to bees from exposure to plant metabolites is considered to be covered by the available field study since the maximum level of a single identified compound was 11% of the total radioactive residue in investigated plant matrices.

5.4. Risk to other arthropod species

Dose-response toxicity studies with *Aphidius rhopalosiphi, Typhlodromus pyri* and *Orius laevigatus* using 'Pyriproxyfen 10 EC' on inert substrate were available to assess the risk to non-target arthropods. Hazard quotients (HQ) for in-field and off-field were calculated for *T. pyri* and *A. rhopalosiphi* in accordance with ESCORT II based on the ER_{50} values obtained in these studies. HQ values for off-field exposure were below 1 for both species regarding both lethal and sub-lethal effects for the use in cotton at 1m from the treated field. In-field HQ values were in the range 2.6 to 9.6 for *T. pyri* based on lethal effects for the different uses. Based on sub-lethal effects HQ values were in the range 6.3 to 24. For *A. rhopalosiphi* the in-field HQ was 2.4 based on sub-lethal effects for the use in tomato in Southern Europe, while for the other uses HQs were <1 for *A. rhopalosiphi.* Effects on *O. laevigatus* did not exceed 30% at the highest dose rate of 450 g a.s./ha, indicating a low risk to this species for all intended uses.

Extended laboratory tests with *T. pyri* protonymphs and *Chrysoperla carnea* larvae using fresh residues on sprayed plants were available. In these studies ER_{50} and LR_{50} values of 205 and >225 g a.s./ha for *T. pyri* and >225 g a.s./ha for *Chrysoperla carnea* were derived. Since the maximum residue level taking into account 2 applications of 112.5 g a.s./ha and a multiple application factor of 1.7 would be 191 g a.s./ha, the in-field risk for all uses was considered to be low.

Given the mode of action of pyriproxyfen it was questioned during the peer review whether the results (addressing only the contact exposure) really reflect the risk from relevant routes of exposure encountered in the field. However, data from literature explored during the expert meeting did not indicate any differences between the exposure routes (contact, oral). Since the effect of 'Pyriproxyfen 10 EC' is by contact action, the RMS considered that the risk assessment to non-target arthropods was sufficiently addressed by the available data. The Member State experts agreed.

5.5. Risk to earthworms

The acute risk to earthworms was considered to be low. TER_a values calculated with an LC_{50corr} from a study using technical pyriproxyfen and the initial PEC_{soil}, taking account of 80% crop interception for tomato and aubergine and 40% interception for cotton, were 9091 for tomato/aubergine in Southern Europe and 8333 for cotton. Since a maximum of 2 applications are foreseen and the DT_{90} in soil was estimated to be ≤100 days, no sublethal/reproduction tests are required.

There were no metabolites of pyriproxyfen detected >10% of applied radioactivity in the soil metabolism studies. Furthermore, considering the large margin of safety for acute toxicity of the parent substance, the risk to earthworms from exposure to soil metabolites was considered to be low even though the DT_{90} from laboratory studies in some cases exceeded 100 days.

5.6. Risk to other soil non-target macro-organisms

No field soil degradation studies with pyriproxyfen were available. However since the DT_{90} was estimated to be <100 days in laboratory studies, no studies on effects on other soil macro-organisms were required. The metabolites 4'-OH-pyr and PYPAC were found at maximum 6.3 and 8.6% applied radioactivity, respectively, in the soil degradation studies. The DT_{90} for both of these metabolites in laboratory studies was >100 days. No studies with earthworms were required for these metabolites, based on the low acute toxicity of the parent substance. Unless the results of the required study on effects on soil micro-organisms (see below) indicate a risk, the risk to other soil macro-organisms can be considered to be low.

5.7. Risk to soil non-target micro-organisms

The microbial effect studies provided by the notifier in the original dossier indicated effects below the Annex VI trigger. The studies were however not accepted by the RMS due to the lack of soil description and some test procedure disagreements. A level 4 data requirement was proposed by the RMS. The notifier submitted a new study, which was assessed, accepted and presented by the RMS in an addendum (December, 2008). However, due to the restrictions laid down in Commission Regulation (EC) No 1095/2007 the study was not peer reviewed, and a data gap was identified at the meeting of Member State experts.

The effects of the soil metabolites 4'-OH-pyr and PYPAC were considered to be covered by the study with pyriproxyfen since the maximum amounts were formed within 14 days.

5.8. Risk to other non-target-organisms (flora and fauna)

No exposure of non-target plants off-field is expected from the use of pyriproxyfen in glasshouses. For the use in cotton a risk assessment was performed based on screening data for 4 plant species, 7 fungal species and 3 insect species. The Guidance Document on Terrestrial Ecotoxicology (European Commission, 2002c) requires at least 6 plant species. However, since pyriproxyfen is an insect juvenile hormone antagonist, herbicidal effects are not expected. No herbicidal effects were observed at an application rate of 8000 g a.s./ha for the four tested plant species. No effects >50% were observed with fungi. (For the risk to insects, see section 5.4).

5.9. Risk to biological methods of sewage treatment

The EC_{50} was determined as >100 mg a.s./L in an activated sludge respiration inhibition test. No adverse effects on biological methods of sewage treatment are therefore expected should pyriproxyfen reach sewage treatment plants.

6. Residue definitions

6.1. Soil

Definition for risk assessment: pyriproxyfen

Definition for monitoring: pyriproxyfen

6.2. Water

6.2.1. Ground water

Definition for exposure assessment: pyriproxyfen, 4-OH-pyr[25] and PYPAC[26]

Definition for monitoring: pyriproxyfen

6.2.2. Surface water

Definition for risk assessment

in surface water: pyriproxyfen, 4-OH-pyr, DPH-pyr[27] and PYPAC

in sediment: pyriproxyfen, 4-OH-pyr and PYPAC

Definition for monitoring: At least pyriproxyfen. A data gap needs to be filled before the definition can be finalised (i.e. DPH-pyr can be excluded from the monitoring definition)

6.3. Air

Definition for risk assessment: pyriproxyfen

Definition for monitoring: pyriproxyfen

6.4. Food of plant origin

Definition for risk assessment: pyriproxyfen

Definition for monitoring: pyriproxyfen

6.5. Food of animal origin

Definition for risk assessment: none proposed, not required for the uses assessed

Definition for monitoring: none proposed, not required for the uses assessed

[25] 4-OH-pyr: 4-(4'-hydroxyphenoxyphenyl) (RS)-2-(2-pryidyloxy)propyl ether
[26] PYPAC: (RS)-2-(2-pyridyloxy)propionic acid
[27] DPH-pyr: 4-hydroxyphenyl (RS)-2-(2-pyridyloxy)propyl ether

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

6.6.1. Soil

Compound (name and/or code)	Persistence	Ecotoxicology
pyriproxyfen	Low to moderate persistence Single first order DT_{50} 2.8-20.4 days (20°C, -10kPa soil moisture)	Low risk to earthworms. Risk to soil non-target micro-organisms has not been addressed.

6.6.2. 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 relevance	Ecotoxicological activity
pyriproxyfen	immobile K_{Foc} 11000-34200 mL/g	No	Yes	Yes	Yes
4-OH-pyr	low to slight mobility K_{Foc} 928-3811 mL/g	No	Not assessed, not required.	Major rat metabolite. Assessment not required.	No
PYPAC	very high mobility K_{Foc} 9-32 mL/g	No	Not assessed, not required.	Rat metabolite. Assessment not required.	No

6.6.3. Surface water and sediment

Compound (name and/or code)	Ecotoxicology
pyriproxyfen	Very toxic to aquatic organisms (E_bC_{50} = 0.094 mg a.s./L). BCF up to 660 in whole fish. The risk assessment was not finalized as the risk to aquatic insects was not addressed.

4-OH-pyr	Very toxic to aquatic organisms (LC_{50} = 0.27 mg a.s./L). The risk to sediment dwelling organisms was considered to be covered by the assessment of pyriproxyfen.
DPH-pyr (water only)	The metabolite was considered to be present in the microcosm study, and the risk was considered covered by the assessment of pyriproxyfen. As the microcosm lack insects, the risk to aquatic insects from DPH-Pyr needs to be addressed. An estimated BCF of 74 indicated a low concern from bioaccumulation.
PYPAC	Harmful to aquatic organisms (E_bC_{50} = 26 mg a.s./L). An estimated BCF of 1.4 indicated a low concern from bioaccumulation. Considered as not ecotoxicological relevant.

6.6.4. Air

Compound (name and/or code)	Toxicology
pyriproxyfen	low acute and repeat-dose toxicity by inhalation (28-day NOAEC of 482 mg/m³)

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

- QC data to support the specification unless the non-relevant impurities in question are removed from the specification (relevant for all uses evaluated, data gap identified by meeting of experts January 2009, proposed submission date unknown, refer to chapter 1)
- Biological activity of the isomers, relative density, spectra (IR, 1H-NMR, mass), water solubility at pH 5, 7 and 9, Henry's law constant, partition coefficient at pH 5, 7 and 9 (relevant for all uses evaluated, data gap identified in the DAR, data submitted and evaluated in the addendum to Volume 3-B1-B5 (December 2008) , refer to chapter 1)
- Oxidising properties of the formulation, identity of the commercial packaging. Depending on the information received further storage stability data may be required to address the interaction of the formulation with the commercial packaging (relevant for all uses evaluated, data gap identified by meeting of experts January 2009, proposed submission date unknown, refer to chapter 1)
- Information on the toxicity and/or on the composition of residues in food commodities with regard to the 2 isomers of pyriproxyfen is technically required to completely address consumer exposure and risk assessment (relevant for all representative uses evaluated; proposed submission date unknown; refer to section 3).
- The risk to aquatic insects from pyriproxyfen needs to be addressed to finalise the aquatic risk assessment (relevant for all representative uses evaluated; data gap identified at PRAPeR 63 meeting, January 2009; proposed submission date unknown; refer to section 5.2)
- The risk to aquatic insects from the metabolite DPH-pyr needs to be addressed to finalise the aquatic risk assessment (relevant for all representative uses evaluated; data gap identified by EFSA while drafting the conclusion; proposed submission date unknown; refer to section 5.2)
- Further studies would be necessary to address the risk to pollinators (relevant for greenhouse uses on tomato and aubergine in Southern Europe; data gap identified at PRAPeR 63 meeting, January 2009; proposed submission date unknown; refer to section 5.3)
- Data to address the effects on soil non-target micro-organisms are required (relevant for all representative uses evaluated; level 4 data requirement; notifier submitted a new study which was assessed, accepted and presented in an addendum (December, 2008) by RMS. The study was however not peer reviewed following Commission Regulation 1095/2007; refer to section 5.7)
- Pyriproxyfen consists of 2 stereo isomers. This needs to be taken into account in the environmental risk assessment. Information on the toxicity and/or on the degradation of the 2 isomers in the environment is needed. (relevant for all representative uses evaluated; open point identified after the expert meeting; proposed submission date unknown; refer to sections 4 and 5).

CONCLUSIONS AND RECOMMENDATIONS

OVERALL CONCLUSIONS

This conclusion was reached on the basis of the evaluation of the representative uses as an insecticide on protected tomato and aubergine and field grown cotton. Full details of the GAP can be found in the list of end points attached at Appendix A.

The representative formulated product for the evaluation was 'Pyriproxyfen 10 EC', an emulsifiable concentrate (EC).

Adequate methods are available to monitor all compounds given in the respective residue definition. Residues in food of plant origin and in soil 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 pyriproxyfen. It should be noted that the residue definition for surface water is provisional.

Sufficient analytical methods 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. The maximum level of two impurities in the specification was not supported by the available data. However, it should be noted that the specification was accepted by mammalian toxicology. The biological activity of the two isomers that make up pyriproxyfen has not been concluded on. Some spectra data, relative density, Henry's law constant, water solubility and partition coefficient were identified as data gaps. It should be noted however that new studies were submitted to address these data gaps but these could not be taken into account in view of the restrictions concerning the acceptance of new studies after the submission of the DAR to EFSA, as laid down in Commission Regulation (EC) No. 1095/2007. Oxidising properties and details of the commercial packaging are outstanding issues for the formulated product.

With regard to the mammalian toxicology, pyriproxyfen was of low acute toxicity in all tested species, neither a skin nor eye irritant, nor a skin sensitizer. After repeated administration, the main target organ was the liver, and slight changes were also observed in the haematological parameters. Negative results were obtained in gene mutation, chromosome aberration and DNA repair tests *in vitro*, as well as *in vivo* in a micronucleus test. No evidence of a carcinogenic potential was observed in long term studies in rats and mice. No adverse effects were observed in the reproductive parameters during a multigeneration study with rats. In the developmental toxicity studies, no teratogenic effect was observed but developmental effects were present in rats at maternal toxic doses. A severel maternal toxicity was observed in both species at the high dose level.

Considering the dog as the most sensitive species, the agreed Acceptable Daily Intake (ADI) was 0.1 mg/kg bw/day based on the 1-year dog study and with the use of a safety factor of 100. The same study was used to derive the Acceptable Operator Exposure Level (AOEL) with a correction for a limited oral absorption (40%), leading to a value of 0.04 mg/kg bw/day. Based on the low toxicity profile of pyriproxyfen, the derivation of an Acute Reference Dose (ARfD) was not considered necessary. The agreed dermal absorption values were 2.5% for the concentrate and 13% for the dilution. The exposure estimates for the operator are below the AOEL without the use of personal protective equipment during outdoor and indoor application in Northern Europe, the indoor application in Southern Europe requires the use of personal protective equipment in order to have an exposure level below the AOEL according to the Dutch model for greenhouse use.

Metabolism of pyriproxyfen was studied in the categories fruit and oilseed crops. The studies indicated pyriproxyfen was more extensively metabolised in cotton than in tomato. Total residues were low in cotton seed and no major compound could be identified. In tomato, however, the major residue was found to be pyriproxyfen, with some minor metabolites detected. Processing data indicated that pyriproxyfen residues did not decay to form any significant degradation product. On the basis of a confined rotational crop study and soil dissipation data it was concluded that significant residues in rotational crops are unlikely to occur. The residue definition for monitoring and risk assessment for the representative uses was proposed as pyriproxyfen alone.

A sufficient number of valid supervised residue trials with pyriproxyfen in tomato and cotton were submitted to support the respective notified uses. According to current guidance, the data on tomato can moreover be used to extrapolate to the notified use on aubergine. On the basis of the available residue data MRLs for pyriproxyfen of 0.3 mg/kg were proposed for tomato and aubergine, respectively, and at the limit of quantification (LOQ) of the analytical method of 0.01 mg/kg for cotton seed.

Residues in livestock feed are not expected to occur at significant levels. The only potential feed item used in current European feeding practice is cotton seed meal. However, residues in cotton seed and cotton seed meal were below the LOQ (0.01 mg/kg).

An estimate of the theoretical maximum daily intake (TMDI) of the consumer with the established MRLs resulted in chronic intakes well below the ADI (<2%) for all considered consumer groups including young children. Based on the low toxicity profile of pyriproxyfen an ARfD was considered not necessary. Therefore, an acute consumer risk assessment is not required.

The information available on the fate and behaviour in the environment is sufficient to carry out an appropriate environmental exposure assessment at the EU level, though no information is available on whether there is differential biodegradation of the two enantiomers of pyriproxyfen. For the applied for intended uses, the potential for groundwater exposure by pyriproxyfen or its soil metabolites 4'-OH-pyr and PYPAC above the parametric drinking water limit of 0.1 µg/L, is low. It should be noted however that the available assessment for groundwater exposure for the protected uses on tomato and aubergine only cover the situation where one crop per calendar year is grown (with 2 applications being made to one of these crops per year). In intensive production systems where it is possible that more than one crop of these fruiting vegetables might be grown in each calendar year, the available assessment would not cover the potential groundwater exposure.

The risk from uptake of pyriproxyfen from the diet, drinking water and secondary poisoning was assessed as low for birds and mammals for all intended uses. Pyriproxyfen was assessed as very toxic to aquatic organisms and not readily biodegradable (R50/53). A higher tier microcosm study was provided to address the risk to aquatic organisms. As insects were missing in the microcosm, a data gap was identified for the applicant to address the risk to aquatic insects before the aquatic risk assessment could be finalised for all intended uses. Application of an assessment factor to the microcosm endpoint should be considered when data on toxicity to insects were available. Bioaccumulation was considered to be of low concern. The risk to bees was assessed as low for the intended use on cotton and on tomato and aubergine in Northern European greenhouses. The risk to pollinators from the insect growth regulator mode of action, however, needs to be addressed further for greenhouse uses on tomato and aubergine in South Europe. The risk to soil non-target micro-organisms was not addressed due to lack of valid studies. A new study was provided by the notifier and

assessed by RMS in an addendum (December 2008). The risk to non-target arthropods, earthworms, soil non-target macro-organisms, non-target plants and biological methods for sewage treatment was assessed as low.

PARTICULAR CONDITIONS PROPOSED TO BE TAKEN INTO ACCOUNT TO MANAGE THE RISK(S) IDENTIFIED

- Use of PPE is required for indoor use in order to have an operator exposure level below the AOEL.

ISSUES THAT COULD NOT BE FINALIZED

- The risk to aquatic insects could not be finalized, since data gaps were identified to address the risk to aquatic insects from both pyriproxfen and the metabolite DPH-pyr.
- The risk to pollinators from the insect growth regulator mode of action needs to be addressed further for greenhouse uses on tomato and aubergine in Southern Europe, as the higher tier risk assessment did not cover the higher application rates in Southern Europe (see section 5.3).
- The risk to soil non-target micro-organisms was not addressed due to lack of valid studies. A new study was provided by the notifier and assessed by the RMS in an addendum (December 2008), however this could not be considered in the peer review in view of the restrictions laid down in Commission Regulation (EC) No. 1095/2007

CRITICAL AREAS OF CONCERN

- The risk to aquatic insects needs to be addressed further for pyriproxyfen and the metabolite DPH-pyr to finalize the aquatic risk assessment. The lack of aquatic insects in the higher tier microcosm study was considered critical, based on the mode of action of pyriproxyfen as an insect growth regulator (see section 5.2).

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APPENDICES

APPENDIX A – LIST OF END POINTS FOR THE ACTIVE SUBSTANCE AND THE REPRESENTATIVE FORMULATION

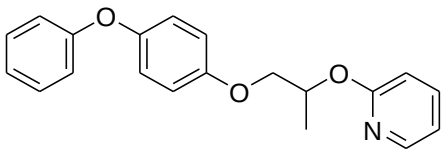
Chapter 2.1 Identity, Physical and Chemical Properties, Details of Uses, Further Information

Identity, Physical and Chemical Properties, Details of Uses, Further Information

Active substance (ISO Common Name)	Pyriproxyfen
Function (*e.g.* fungicide)	Insecticide
Rapporteur Member State	The Netherlands

Identity (Annex IIA, point 1)

Chemical name (IUPAC)	4-phenoxyphenyl (RS)-2-(2-pyridyloxy)propyl ether
Chemical name (CA)	2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy]pyridine
CIPAC No	715
CAS No	95737-68-1
EEC No (EINECS or ELINCS)	429-800-1 (ELINCS)
FAO Specification (including year of publication)	FAO specification 715/TC (July 2006): Minimum purity of pyriproxyfen: 970 g/kg
Minimum purity of the active substance as manufactured (g/kg)	970 g/kg racemic mixture

Identity of relevant impurities (of toxicological, environmental and/or other significance) in the active substance as manufactured (g/kg)	Toluene maximum level 5 g/kg
Molecular formula	$C_{20}H_{19}NO_3$
Molecular mass	321.37u
Structural formula	

Physical-chemical properties (Annex IIA, point 2)

Melting point	Purity 100%: 48.0-50.0 °C
Boiling point	Purity 99.7%: 318 °C
Temperature of decomposition	No decomposition up to 318 °C under N_2 atmosphere.
Appearance	Purity 100%: granular white solid Technical material: pale yellowish white solid at 20°C
Surface tension	Not applicable (water solubility <1 mg/L)

Vapour pressure (in mBar and Pa, state temperature)	Pure material: <1.33 x 10^{-5} Pa at 22.81 °C
Henry's law constant (Pa m3 mol –1)	Open
Solubility in water (g/l or mg/l at 20 °C)	Open
Solubility in organic solvents (in g/L or mg/L)	Purity 97.9%, at 20 °C: n-Heptane : 25 to 29 g/L 1,2-Dichloroethane : >1000 g/L Methanol : 25 to 29 g/L Acetone : >1000 g/L p-Xylene : >1000 g/L Ethyl acetate : >1000 g/L.
Partition co-efficient (log POW) (state temperature)	open
Dissociation constant	Not determined due to the low water solubility of the test substance A pKa of 6.87 was obtained from Pkalc version 5.0 (module in PALLAS version 3.0; estimation performed by RMS).

UV / VIS absorption (max.) (if absorption >290 nm state ε at wavelength)	UV/Vis-spectrum is determined in water/methanol mixture (10:90 v/v) Acidic: 278 nm (ε = 10354 L·mol-1·cm-1) Neutral: 271 nm (ε = 6649 L·mol-1·cm-1) Basic: 271 nm (ε = 6749 L·mol-1·cm-1)
Flammability and auto-flammability	Purity 97.9%: Flammability: not highly flammable. Auto-ignition temperature: no auto-ignition up to 400 °C
Explosive properties	Not explosive (DSC analysis; 97.9% TGAI)
Oxidising properties	Not oxidizing (theoretical assessment)

Summary of representative uses evaluated (pyriproxyfen)*

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			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 applications (min)	kg as/hL min max	water L/ha min max	kg as/ha min max		
Tomato (greenhouse)	South Europe	Pyriproxyfen 10 EC	G	Greenhouse and cotton whitefly	EC	100 g/L	Foliar spray (High Volume Spraying)	BBCH 89	1-2	10 days	0.005-0.0075	1000-1500	0.05-0.1125	3	First application: as soon as adults are observed [1]
Tomato (greenhouse)	North Europe	Pyriproxyfen 10 EC	G	Greenhouse and cotton whitefly	EC	100g/L	Foliar spray (High Volume Spraying)	BBCH 89	1-2	10 days	0.002-0.003	800-1200	0.02-0.03	3	
Aubergine (greenhouse)	South Europe	Pyriproxyfen 10 EC	G	Greenhouse and cotton whitefly	EC	100g/L	Foliar spray (High Volume Spraying)	BBCH 89	1-2	10 days	0.005-0.0075	1000-1500	0.05-0.1125	3	
Aubergine (greenhouse)	North Europe	Pyriproxyfen 10 EC	G	Greenhouse and cotton whitefly	EC	100g/L	Foliar spray (High Volume Spraying)	BBCH 89	1-2	10 days	0.002-0.003	800-1200	0.02-0.03	3	

Cotton	South Europe	Pyriproxyfen 10 EC	F	Cotton whitefly	EC	100g/L	Foliar spray (High Volume Spraying)	BBCH 78-79	1	n.a.	0.009-0.015	500-800	0.075	n.a.	

[1] A high risk and data gaps were identified in Section 5.

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

Chapter 2.2 – Methods of Analysis

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

Technical as (principle of the method)	Dissolution in methanol containing internal standard (*p*-benzyldiphenyl) followed by reversed phase HPLC-UV analysis.
Impurities in technical as (principle of the method)	GC-FID and HPLC-UV
Plant protection product (principle of the method)	Dissolution in methanol followed by reversed phase HPLC-MS analysis.

Analytical methods for residues (Annex IIA, point 4.2)

Residue definitions for monitoring purposes

Food of plant origin		Pyriproxifen
Food of animal origin		Not required
Soil		Pyriproxifen
Water	surface	Pyriproxifen (provisional)
	drinking/ground	Pyriproxifen
Air		Pyriproxifen

Monitoring/Enforcement methods

Analytical methods for residues (Annex IIA, point 4.2)

Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	Samples were extracted and analysed according to DFG method S19. Cucumber samples were extracted with acetone/water 2/1 (v/v) partitioned with ethylacetate/cyclohexane, evaporated and redissolved in ethylacetate/cyclohexane. Cotton seed and olive samples were extracted with acetone/acetonitrile, evaporated and redissolved in ethylacetate/cyclohexane. After gel permeation chromatography samples were reconstituted in ethyl acetate followed by GC-MS-analysis. LOQ (pyriproxyfen): 0.01 mg/kg (cucumber fruit, olives, cotton seed).
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	Not applicable.
Soil (principle of the method and LOQ)	Multi method DFG method S19: Soil was extracted with acetone:water, partitioned with ethylacetate/cyclohexane, redissolved in ethylacetate/cyclohexane and subjected to gel permeation chromatography followed by reconstitution in ethyl acetate. After addition of iso-octane, the residue was passed through a silica gel column using subsequently hexane/toluene, toluene and toluene-acetone. The toluene-acetone eluate was evaporated to dryness and the residue redissolved in toluene before analysis by GC-NPD (confirmation by GC-MS). LOQ (pyriproxyfen): 0.01 mg/kg.
Water (principle of the method and LOQ)	Tap water: 1L of tap water, distilled water, air and acetone were passed through a SPE C18 column. Surface water: 1L of surface water, distilled water, air and hexane were passed through a SPE C18 column. The acetone or hexane eluate was evaporated and the residue was reconstituted in toluene followed by GC-NPD analysis (confirmation by GC-MS). LOQ tap water (pyriproxyfen): 0.1 µg/L LOQ surface water (pyriproxyfen): 0.01 µg/L.

Air (principle of the method and LOQ)	Air sampling cartridges (Tenax adsorption tubes) were extracted with toluene and analysed by GC-NPD (confirmation with GC-MS). LOQ (pyriproxyfen): 1.0 µg/m^3 (~20°C, ~30% rH and ~35°C, ≥ 80% rH).
Body fluids and tissues (principle of the method and LOQ)	Not required, not a toxic or very toxic compound.

Classification and proposed labelling (Annex IIA, point 10)

With regard to physical and chemical data	No classification is proposed

Chapter 2.3 Impact on Human and Animal Health

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

Rate and extent of oral absorption	40% based on radiolabel recovered in urine, cage wash and bile within 48 h.
Distribution	Limited (0.1-0.3% in tissues); highest residues in fat and liver.
Potential for accumulation	No evidence of accumulation
Rate and extent of excretion	Rapid: mainly faecal (46-74% in 24h) and urinary (3-9% in 24 h)
Metabolism in animals	Extensively metabolised
Toxicologically relevant compounds (animals and plants)	Pyriproxyfen
Toxicologically relevant compounds (environment)	Pyriproxyfen

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral	> 5000 mg/kg bw	
Rat LD_{50} dermal	> 2000 mg/kg bw	
Rat LC_{50} inhalation	> 1.3 mg/L (max. attainable conc.) (4 h; whole body)	
Skin irritation	Non-irritant	
Eye irritation	Non-irritant	
Skin sensitisation	Non-sensitiser (M&K)	

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect	Liver, red blood cells	
Relevant oral NOAEL	10 mg/kg bw/d (1-yr, dog) 24 mg/kg bw/d (13-wk and 6-mo, rat)	
Relevant dermal NOAEL	1000 mg/kg bw/d (21-d, 6h/d, rat)	
Relevant inhalation NOAEL	482 mg/m^3 (4-wk, rat, 4h/day, whole body)	

Genotoxicity (Annex IIA, point 5.4)

No genotoxic potential	

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

Target/critical effect	Liver (rat, mouse); kidney (mouse)	
Relevant NOAEL	27.2 mg/kg bw/d (104-wk, rat) 16.4 mg/kg bw/d (78-wk, mice)	
Carcinogenicity	No carcinogenic potential	

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction toxicity

Reproduction target / critical effect	No reproduction effects. Offspring effects: decreased pup weights at parental toxic doses. Parental effects: increased liver weight	
Relevant parental NOAEL	13.3 mg/kg bw/d	
Relevant reproductive NOAEL	333.3 mg/kg bw/d (highest dose tested)	
Relevant offspring NOAEL	66.7 mg/kg bw/d	

Developmental toxicity

Developmental target / critical effect	No teratogenic effects. Developmental effects in rats: increased number of foetuses with an opening of the foramen transversarium of the 7th cervical vertebra at maternal toxic doses. No developmental effects in rabbits. Maternal effects in rats: mortality, clinical signs Maternal effects in rabbits: mortality, clinical signs, increased abortions	
Relevant maternal NOAEL	Rat: 100 mg/kg bw/d Rabbit: 100 mg/kg bw/d	
Relevant developmental NOAEL	Rat: 100 mg/kg bw/d Rabbit: 300 mg/kg bw/d	

Neurotoxicity (Annex IIA, point 5.7)

Acute neurotoxicity	No data, no concern from other studies	
Repeated neurotoxicity	No data, no concern from other studies	
Delayed neurotoxicity	No data available – not required	

Other toxicological studies (Annex IIA, point 5.8)

Mechanism studies	No data available – not required
Studies performed on metabolites or impurities	No data available – not required

Medical data (Annex IIA, point 5.9)

No evidence of toxicological concern from medical surveillance of manufacturing plant personnel. No reported cases of poisoning incidents.

Summary (Annex IIA, point 5.10)	**Value**	**Study**	**Safety factor**
ADI	0.1 mg/kg bw/d	1-year, dog	100
AOEL	0.04 mg/kg bw/d	1-year, dog	100*
ARfD	Not necessary, not allocated		

* + correction for 40% oral absorption

Dermal absorption (Annex IIIA, point 7.3)

Formulation (Pyriproxyfen 10 EC)	2.5% for the undiluted formulation and 13% for the spray dilution based on *in vitro* dermal absorption data with human skin

Exposure scenarios (Annex IIIA, point 7.2)

Operator	Use	Model	No PPE	PPE
	outdoor	UK POEM	74	10
		German	18	14
	indoor North	NL greenhouse	29	4
	South		108	15
Workers	Use in cotton: 28% of AOEL without PPE (EUROPOEM II) Use in tomato and aubergine: 11% of AOEL in Northern Europe and 42% of AOEL in Southern Europe, without PPE (EUROPOEM II).			
Bystanders	Use in cotton: <1% of AOEL (EUROPOEM II) Bystanders should not be allowed in greenhouses during application.			

Classification and proposed labelling with regard to toxicological data (Annex IIA, point 10)

	RMS/peer review proposal
Substance classified (name)	none

Chapter 2.4 – Residues

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

Plant groups covered	Fruits (tomato, apple), pulses and oil seeds (cotton)
Rotational crops	Radish, lettuce, wheat
Plant residue definition for monitoring	Pyriproxyfen
Plant residue definition for risk assessment	Pyriproxyfen
Conversion factor (monitoring to risk assessment)	1

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

Animals covered	Goat, hen.
Animal residue definition for monitoring	Not relevant for notified uses. (No significant intake; no accumulation of residues in edible animal products expected).
Animal residue definition for risk assessment	Not relevant for notified uses. (No significant intake; no accumulation of residues in edible animal products expected).
Conversion factor (monitoring to risk assessment)	Not applicable.
Metabolism in rat and ruminant similar (yes/no)	Yes
Fat soluble residue: (yes/no)	No

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

Total radioactive residue (TRR): Plantback interv. 30 d: lettuce: 0.007 mg eq/kg radish leaf: 0.011 mg eq/kg radish root: 0.005 mg eq/kg wheat forage: 0.011 mg eq/kg wheat grain: 0.081 mg eq/kg wheat straw: 0.059 mg eq/kg wheat chaff: 0.082 mg eq/kg (application to bare soil at 0.198 kg as/ha)

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

Pyriproxyfen residues in tomato was stable during storage at -18°C for a period of 12 months.
Pyriproxyfen residues in cotton seed, cotton gin trash and crude oil were stable during storage at -20°C for a period of 395, 231 and 32 days, respectively.
PYPAC residues were stable in cotton seed and crude oil during storage at -20°C for a period of 380 and 32 days, respectively. DPH-PYR residues in cotton gin trash were not stable during storage at -20°C for a period of 89 days.

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:	Poultry:	Pig:
	No	No	No
Muscle Liver Kidney Fat Milk Eggs	No studies submitted and no studies necessary for the notified uses (tomato, aubergine, cotton).		

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 mg/kg pyriproxyfen	Recommendation/comments	MRL mg/kg	STMR mg/kg	HR
Tomato fruits	SMS	1 x 0.05 1 x 0.06 1 x 0.08 1 x 0.09 2 x 0.11 1 x 0.17 1 x 0.18	LOQ is 0.01 mg/kg. Application in greenhouse (results also valid for NMS). Extrapolation to aubergine (greenhouse) possible.	0.3[1]	0.10[1]	0.18
Cotton seed	SMS	2 x <0.01	LOQ is 0.01 mg/kg.	0.01*	0.01*	0.01

1. Also valid for aubergine.

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

Note: Data on the actual ratio of pyriproxifen isomers in the terminal residue on the crops is technically required for a sound risk assessment (refer to chapter 3.3 of the EFSA conclusion).

Results presented here-below premise that pyriproxifen crop residues consisted of the same ratio of isomers as tested in the toxicological studies.

ADI	0.1 mg/kg bw/day
TMDI (% ADI) according to WHO European diet	1.5 % (WHO cluster diet B)
TMDI (% ADI) according to national (to be specified) diets	EFSA PRIMo: 0.9% French toddler and German child 0.8% UK Toddler and NL child
IEDI (WHO European Diet) (% ADI)	not required
NEDI (specify diet) (% ADI)	not required
Factors included in IEDI and NEDI	not applicable
ARfD	none allocated
IESTI (% ARfD)	not applicable
NESTI (% ARfD) according to national (to be specified) large portion consumption data	not applicable
Factors included in IESTI and NESTI	not applicable

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

Crop/processed crop	Number of studies	Transfer factor
Tomato peeled fruit	1	<0.17
Tomato peels	1	7.3
Tomato canned fruit	2	<0.2

Tomato fruit juice	2	<0.2
Tomato purée	2	0.67-1.8
Tomato ketchup	1	0.67
Cotton seed meal	1	<0.2
Cotton seed hulls	1	<0.2
Cotton seed crude oil	1	0.2
Cotton seed refined oil	1	0.2

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

Proposed MRLs	Tomato, aubergine: 0.3 mg/kg Cotton seed : 0.01* mg/kg

Chapter 2.5 – Fate and Behaviour in the Environment

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

Mineralization after 100 days ‡	11-42.5% after 90-94 d, [U-^{14}C-phenoxyphenyl] (n=2) (24-61 % after 91-94 d, [pyridyl-2,6-^{14}C] (n=6)
Non-extractable residues after 100 days ‡	51-58 % after 90-122 d, [U-^{14}C-phenoxyphenyl] (n=6) 30-49 % after 91-122 d, [pyridyl-2,6-^{14}C] (n=2)
Metabolites requiring further consideration ‡ - name and/or code, % of applied (range and maximum)	4'-OH-pyriproxyfen – 0.9-6.3 % at 1-14 d (n= 6) PYPAC – 1.0-8.6 % at 1-14 d (n= 6) [^{14}C-phenoxyphenyl] & [^{14}C-pyridyl] labels

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

Anaerobic degradation ‡

Mineralization after 100 days	No studies submitted
Non-extractable residues after 100 days	-
Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	-

Soil photolysis ‡

Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	PYPAC – max 13.1 % at 10 d (n=1) [^{14}C-pyridyl-2,6] label $DT_{50\ photolysis}$: ca. 15.8-27.5 days at 43°N for [^{14}C-pyridyl-2,6] label and [^{14}C-phenyl label resp.

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

Laboratory studies ‡

Parent	Aerobic conditions						
Soil type	X[28]	pH	t. °C / % MWHC	DT_{50} /DT_{90} (d)	DT_{50} (d) 20°C pF2/10kPa	St. (r^2)	Method of calculation
Sandy loam[#]		6.5[2]	25 °C / 75 % FC	8.3 / 28	9.8	0.997	SFO
Sandy clay loam[#]		5.7[2]	25 °C / 75 % FC	17 / 54	20.4	0.87	SFO
California Sandy loam[#]		7.6	25 °C / 75% FC	9.7 / 33	11.4	0.97	SFO
PT102 Sandy loam (PYR-label)		6.7[3]	20 °C / 45% MWHC	4.4 / 15	4.4	0.99	SFO
PT103 Sandy loam (PYR-label)		4.9[3]	20 °C / 45% MWHC	6.1 / 20	6.1	0.96	SFO
Silt loam (PYR-label)		6.2[3]	20 °C / 45% MWHC	3.7 / 12	3.7	0.94	SFO
Clay loam (PYR-label)		7.3[3]	20 °C / 45% MWHC	2.8 / 9.2	2.8	0.95	SFO
Geometric mean/Median					6.7 / 6.1		

[#] arith. mean of 2 labels
[2] pH H2O
[3] pH $CaCl_2$

4'-OH-pyriproxyfen (PYR-label)	Aerobic conditions							
Soil type	X[1]	pH	t. °C / % MWHC	DT_{50}/ DT_{90} (d)	f. f. k_{dp}/k_f	DT_{50} (d) 20°C pF2/10kPa	St. (r^2)	Method of calculation
Sandy loam		7.6	25 °C / 75 % FC	47 / 157		57.2	0.86	SFO*
PT102 Sandy loam (PYR-label)		6.7[3]	20 °C / 45% MWHC	28 / 92		28	0.74	SFO*

[28] X This column is reserved for any other property that is considered to have a particular impact on the degradation rate.

PT103 Sandy loam (PYR-label)		4.9[3]	20 ºC / 45% MWHC	n.c.				
Silt loam (PYR-label)		6.2[3]	20 ºC / 45% MWHC	24 / 78		24	0.85	SFO*
Clay loam (PYR-label)		7.3[3]	20 ºC / 45% MWHC	30 / 98		30	0.82	SFO*
Geometric mean Arithm. mean				31.2 / 102		32.8 34.8		

* these values are decline rates (represent the result of the sum of formation and degradation rate constants) estimated from the time point of the maximum observed concentration in studies where pyriproxyfen was dosed.

PYPAC (PYR-label)	Aerobic conditions							
Soil type	X[1]	pH	t. ºC / % MWHC	DT_{50}/ DT_{90} (d)	f. f. k_{dp}/k_f	DT_{50} (d) 20°C pF2/10kPa	St. (r^2)	Method of calculation
Sandy loam		7.6	25 ºC / 75 % FC	25 / 79		29.4	0.97	SFO*
California Sandy loam[#]		7.6	25 ºC / 75% FC	14 / 46		17.2	0.989	SFO*
PT103 Sandy loam		4.9[3]	20 ºC / 45% MWHC	0.4 / 1.3		0.4	0.9	SFO*
Geometric mean Arithm. mean				5.2 / -		5.9 15.7		

* these values are decline rates (represent the result of the sum of formation and degradation rate constants) estimated from the time point of the maximum observed concentration in studies where pyriproxyfen was dosed.

Field studies ‡

Parent	Aerobic conditions								
Soil type (indicate if bare or cropped soil was used).	Location (country or USA state).	X[1]	pH	Depth (cm)	DT_{50} (d) actual	DT_{90}(d) actual	St. (r^2)	DT_{50} (d) Norm.	Method of calculation
Silt loam	Mississipi		5.9	0-30	3.5	12	0.92	-	SFO
Loamy sand	Washington		7.6	0-30	5.9	20	0.93	-	SFO
Loamy sand	New York		6	0-7.5	3.5	12	0.69	-	SFO
Geometric mean					4.2				

pH dependence ‡ (yes / no) (if yes type of dependence)	none
Soil accumulation and plateau concentration ‡	Not calculated, not required

Soil adsorption/desorption (Annex IIA, point 7.1.2)

Parent ‡							
Soil Type	OC %	Soil pH	Kd (mL/g)	Koc (mL/g)	K_F (mL/g)	$K_F$oc (mL/g)	1/n
Sandy loam	1.0	8.0	-	-	126	12600	1.1
Silt loam	0.6	7.0	-	-	174	26900	1.1
Silty clay loam	0.8	7.8	-	-	282	34200	1.2
Loam	2.9	7.0	-	-	324	11000	1.2
Arithmetic mean					227	21175	1.15
pH dependence, Yes or No			no				

4’-OH-Pyr ‡							
Soil Type	OC %	Soil pH	Kd (mL/g)	Koc (mL/g)	K_F (mL/g)	$K_F$oc (mL/g)	1/n
Sandy loam	0.6	6.9	-	-	21.5	3811	0.85
Silt loam	1.1	6.9	-	-	32.8	3062	0.77
Clay loam	1.2	7.9	-	-	11.5	921	1.0
Arithmetic mean					21.9	2598	0.87
pH dependence (yes or no)			No				

PYPAC ‡							
Soil Type	OC %	Soil pH	Kd (mL/g)	Koc (mL/g)	K_F (mL/g)	$K_F$oc (mL/g)	1/n
Sandy loam	0.6	6.9	-	-	0.12	21	1.0
Silt loam	1.1	6.9	-	-	0.34	32	1.0
Clay loam	1.2	7.9	-	-	0.11	9	1.2
Arithmetic mean					0.19	20.7	1.07
pH dependence (yes or no)			No				

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

Column leaching ‡	Eluation (mm): 69 mm/day simulated rainfall Time period (d): 7.5 d
	Leachate: 0.1 and 2.8 % total residues/radioactivity in leachate 0 % active substance, 0 % Met I, 0 % Met VII ~5 % total residues/radioactivity retained in top 5 cm
Aged residues leaching ‡	Aged for (d): 9 d Time period (d): 15 hours Eluation (mm): 782 mm/day simulated rainfall
	Analysis of soil residues post ageing (soil residues pre-leaching): 39-48 % active substance for [U-phenoxyphenyl-14C] and [2,6-pyridyl-14C] label respectively, 5.1-3.4 % 4'-OH-Pyr for [U-phenoxyphenyl-14C] and [2,6-pyridyl-14C] label respectively, 1.8 % PYPAC for [2,6-pyridyl-14C] label, 1.4-0.8% DPH-Pyr for [U-phenoxyphenyl-14C] and [2,6-pyridyl-14C] label respectively.
	Leachate: 1-7.6 % total residues/radioactivity in leachate for [U-phenoxyphenyl-^{14}C] and [2,6-pyridyl-^{14}C] label respectively <0.8 % active substance, <0.8 %4'-OH-Pyr, 6.5 % PYPAC for [2,6-pyridyl-^{14}C] label only. ~88% total residues/radioactivity retained in top 9 cm
Lysimeter/ field leaching studies ‡	No data submitted, not required

PEC (soil) (Annex IIIA, point 9.1.3)

Parent Method of calculation	DT_{50} (d): 25 days; max. Lab (20 ºC)(no moisture correction) Kinetics: SFO

Application data	Crop: Tomato/Aubergine Depth of soil layer: 5 cm. Soil bulk density: 1500 kg/m^3 % plant interception: 80% Number of applications: 2 Interval (d): 10 d Application rate(s): 30 g as/ha (NE); 112.5 g as/ha (SE)

PEC$_{(s)}$ (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual		Multiple application Time weighted average	
			NE	SE	NE	SE
Initial	-		0.015	0.055	-	-
Short term 24h	-	-	0.014	0.053	0.014	0.054
2d	-	-	0.014	0.052	0.014	0.053
4d	-	-	0.013	0.049	0.014	0.052
Long term 7d	-	-	0.012	0.045	0.013	0.050
28d	-	-	0.008	0.031	0.011	0.041
50d	-	-	0.007	0.025	0.010	0.038
100d	-	-	0.004	0.014	0.008	0.030

Parent Method of calculation	DT$_{50}$ (d): 25 days; max. Lab (20 ºC)(no moisture correction) Kinetics: SFO
Application data	Crop: Cotton Depth of soil layer: 5 cm. Soil bulk density: 1500 kg/m^3 % plant interception: 75% Number of applications: 1 Application rate(s): 75 g as/ha (SE)

PEC$_{(s)}$ (mg/kg)	Single application Actual		Single application Time weighted average		Multiple application Actual	Multiple application Time weighted average
	NE	SE	NE	SE		•
Initial	n.a.	0.025	n.a.	-	n.a.	• n.a.
Short term 24h		0.024		0.025	-	-
2d		0.024		0.024	-	-
4d		0.022		0.024	-	-
Long term 7d		0.021		0.023	-	-
28d		0.014		0.019	-	-
50d		0.012		0.017	-	-
100d		0.006		0.014	-	-

4'-OH-Pyriproxyfen Method of calculation	Molecular weight relative to the parent: 1.05 DT_{50} (d): 70 days; maximum DT_{50lab}, 20°C (no moisture correction) Kinetics: SFO Maximum % of formation: 6.3
Application data	Crop: Tomato/Aubergine % plant interception: 80% Number of applications: 2 Interval (d): 10 d Application rate assumed: 1.98 g as/ha NE and 7.44 g as/ha SE (assumed 4'-OH-Pyr is formed at a maximum of 6.3 % of the applied dose)

PEC$_{(s)}$ (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual		Multiple application Time weighted average	
			NE	SE	NE	SE
Initial	n.a.	-	0.001	0.004	-	-
Short term 24h	-	n.a.	0.001	0.004	0.001	0.004
2d	-	-	0.001	0.004	0.001	0.004
4d	-	-	0.001	0.004	0.001	0.004
Long term 7d	-	-	0.001	0.003	0.001	0.004
21d	-	-	0.001	0.003	0.001	0.003
28d	-	-	0.000	0.003	0.000	0.003
50d	-	-	0.000	0.002	0.000	0.003
100d	-	-	0.000	0.000	0.00	0.002

4'-OH-Pyr Method of calculation	Molecular weight relative to the parent: 1.05 DT_{50} (d): 70 days; maximum DT_{50lab}, 20°C (no moisture correction) Kinetics: SFO Maximum % of formation: 6.3
Application data	Crop: Cotton % plant interception: 75% Number of applications: 1 Application rate assumed: 4.96 g as/ha NE and 7.44 g as/ha SE (assumed 4'-OH-Pyr is formed at a maximum of 6.3 % of the applied dose)

PEC$_{(s)}$ (mg/kg)	Single application Actual		Single application Time weighted average		Multiple application Actual	Multiple application Time weighted average
	NE	SE	NE	SE		•
Initial	n.a.	0.0024	n.a.	-	n.a.	-
Short term 24h		0.0024		0.0024	-	n.a.
2d		0.0024		0.0024	-	-
4d		0.0024		0.0024	-	-

Long term 7d		0.0024		0.0024		
28d		0.001		0.001	-	• -
50d		0.001		0.001	-	-
100d		0.001		0.001	-	-

PYPAC Method of calculation	Molecular weight relative to the parent: 0.52 DT_{50} (d): 37 days; maximum DT_{50lab}, 20°C (no moisture correction) Kinetics: SFO Maximum % of formation: 8.6
Application data	Crop: Tomato/Aubergine % plant interception: 80% Number of applications: 2 Interval (d): 10 d Application rate assumed: 1.34 g as/ha NE and 5.03 g as/ha SE (assumed PYPAC is formed at a maximum of 8.6 % of the applied dose)

$PEC_{(s)}$ (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual		Multiple application Time weighted average	
			NE	SE	NE	SE
Initial	n.a.	n.a.	0.002	0.007	-	-
Short term 24h			0.002	0.007	0.002	0.007
2d			0.002	0.006	0.002	0.007
4d			0.002	0.006	0.002	0.006
Long term 7d			0.002	0.006	0.002	0.006
21d			0.001	0.004	0.001	0.006
28d			0.001	0.004	0.001	0.005
50d			0.001	0.003	0.001	0.004
100d			0.000	0.001	0.001	0.003

PYPAC Method of calculation	Molecular weight relative to the parent: 0.52 DT_{50} (d): 37 days; maximum DT_{50lab}, 20°C (no moisture correction) Kinetics: SFO Maximum % of formation: 8.6

Application data	Crop: Cotton % plant interception: 75% Number of applications: 1 Application rate assumed: 3.35 g as/ha (assumed PYPAC is formed at a maximum of 8.6 % of the applied dose)

PEC$_{(s)}$ (mg/kg)	Single application Actual		Single application Time weighted average		Multiple application Actual	Multiple application Time weighted average
	NE	SE	NE	SE		•
Initial	n.a.	0.001	n.a.	-	n.a.	n.a.
Short term 24h		0.001		0.001	-	-
2d		0.001		0.001	-	-
4d		0.001		0.001	-	-
Long term 7d		0.001		0.001	-	-
28d		0.001		0.001	-	-
50d		0.001		0.001	-	-
100d		<0.001		0.001	-	-

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

Hydrolytic degradation of the active substance and metabolites > 10 % ‡	pH 4 (50 ºC): stable
	pH 7: at 50 °C stable
	pH 9: at 50 °C stable
Photolytic degradation of active substance and metabolites above 10 % ‡	DT_{50} : 11.5 Natural light, 43°N; DT_{50} 11.5 days (8.5 – 14.5 d; n=2) Met PYPA: 70 %AR (14 d) Assumed (polymerised) phenolic structures: maximum 60% AR (14 d)
Quantum yield of direct phototransformation in water at Σ > 290 nm	Φ = 0.08661
Readily biodegradable ‡ (yes/no)	not ready biodegradable

Degradation in water / sediment

Parent	Distribution (eg max in water *53-74%* at time 0. Max. sed *45-48%* 1-2 days)									
Water / sediment system	pH water phase	pH sed	t. °C	DT_{50}-DT_{90} whole sys.	St. (r^2)	DT_{50}-DT_{90} water	St. (r^2)	DT_{50}- DT_{90} sed	St. (r^2)	Method of calculation
Clay loam[#]	~8.5	~7.5	20	5.4 – 17.9	0.98	1.7 – 5.4*	0.98	30.6 – 102*	0.83	SFO
Sandy loam[#]	~8.0	~6.5	20	7.8 – 26.1	0.85	1.4 – 4.6*	0.96	37.7 – 125*	0.96	SFO
Geometric mean Arithm. mean				6.5 – 21.6 6.6 - 22						

[#] mean of 2 -labels

* The DT_{50} and $_{90}$ indicated for water and sediment separately are observed dissipation values

4'-OH-Pyr[1]	Distribution (eg max in water 4.8% after 14 d. Max. sed 14.8 % after 50 d)									
Water / sediment system	pH water phase	pH sed	t. °C	DT_{50}-DT_{90} whole sys.	St. (r^2)	DT_{50}-DT_{90} water	r^2	DT_{50}- DT_{90} sed	St. (r^2)	Method of calculation
Clay loam (applied as a.s.)	~8.5	~7.5	20	21.6-71.8	0.99	1.9-6.5	0.94	21.5-71.4	0.99	1st order Decline from max. occurrence
Sandy loam (applied as a.s.)	~8.0	~6.5	20	37.2-123	0.98	n.c.		41.5-138	0.99	1st order Decline from max. occurrence
Clay loam (applied as met.)	~8.5	~7.2	20	1.7 – 5.6	0.83	0.4-1.4	0.99	17.3-57.5	0.95	1st order
Sandy loam (applied as met.)	~8.0	~6.5	20	0.8-2.7	0.98	0.7-2.4	0.97	n.c	na	1st order
Geometric mean / Arithm. mean				5.7 – 19.1 15.3-50.8						

[1] phenyl-label only

DPH-Pyr	Distribution (eg max in water 11.8% after 2 d. Max. sed 4.3 % after 50 d)									
Water / sediment system	pH water phase	pH sed	t. °C	DT_{50}-DT_{90} whole sys.	St. (r^2)	DT_{50}-DT_{90} water	r^2	DT_{50}- DT_{90} sed	St. (r^2)	Method of calculation
Clay loam	~8.5	~7.5	20	n.c.						
Sandy loam	~8.0	~6.5	20	n.c.						
Clay loam (applied as 4'-OH-Pyr)	~8.5	~7.2	20	<4 - >73	na	<4	na	n.c.	na	1st order
Sandy loam (applied as 4'-OH-Pyr)	~8.0	~6.5	20	n.c.	na	4 – 13.2	0.97	nc	na	
Geometric mean/median										

PYPAC	Distribution (eg max in water 23.6% after 100 d. Max. sed 7.6 % after 100 d)									
Water / sediment system	pH water phase	pH sed	t. °C	DT_{50}-DT_{90} whole sys.	St. (r^2)	DT_{50}-DT_{90} water	r^2	DT_{50}- DT_{90} sed	St. (r^2)	Method of calculation
Clay loam[1] (applied as met.)	~8.5	~7.5	20	62.9-209	0.96	33.9-113	0.89	38.3-127	0.93	1st order
Sandy loam[1] (applied as met.)	~8.0	~6.5	20	11.6-38.4	0.98	9.1-30.1	0.99	17-56.3	0.70	1st order
Geometric mean/ Arithm.mean				27 – 89.6 37.3-124						

[1] phenyl-label only

Mineralization and non extractable residues					
Water / sediment system	pH water phase	pH sed	Mineralization x % after 100 d. (end of the study).	Non-extractable residues in sed. Max x % after x d	Non-extractable residues in sed. Max x % after 100 d (end of the study)
Clay loam	~8.5	~7.5	11-25% (pyridyl/phenyl label)	-	31-39% (pyridyl/phenyl label)
Sandy loam	~8.0	~6.5	36-53% (pyridyl/phenyl label)	-	37-51% (pyridyl/phenyl label)

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

Parent	Version control no. of FOCUS calculator: 1.1
Parameters used in FOCUSsw step 1 and 2	Molecular weight (g/mol): 312.5 Water solubility (mg/L): 0.367 mg/L K_{OC}/K_{OM} (L/kg): 21175 L/kg DT_{50} soil (d): 10 days (Lab SFO) DT_{50} water/sediment system (d): 6.6 days DT_{50} water (d): 1.6 days DT_{50} sediment (d): 34.2 days Crop interception (%): 50% tomato/aubergine, 75% cotton No runoff/drainage for glasshouse applications FOCUS STEP 2 (for greenhouse applications a worst case total surface water loading of 0.1% is assumed whereas the default drift value in STEP 2 is 2.38% (therefore the STEP 2 results were divided by 23.8))
Parameters used in FOCUSsw step 3 (if performed)	Version control no.'s of FOCUS software: 1.1 Vapour pressure: 1.3E-05 Pa Kom/Koc: 21175 L/kg 1/n: 1.15
Application rate	Crop: Cotton Crop interception: 75% at step 2 calculated by the model at step 3 Number of applications: 1 Interval (d): - Application rate(s): 75 g as/ha Application window: June-Sep

Parent: pyriproxyfen

FOCUS STEP 1 Scenario Cotton (SE)	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
	0 h	1.5449	-	181.19	
	24 h	0.7912	1.1681	167.53	174.31
	2 d	0.7123	0.9595	150.83	166.67
	4 d	0.5773	0.8010	122.25	151.36
	7 d	0.4213	0.6700	89.214	131.43
	14 d	0.2020	0.4842	42.772	97.303
	21 d	0.0968	0.3704	20.506	74.964
	28 d	0.0464	0.2950	9.8312	59.853
	42 d	0.0107	0.2048	2.2597	41.619
	50 d	0.0046	0.1732	0.9754	35.204
	100 d	0.0000	0.0870	0.0051	17.695

FOCUS STEP 2 Scenario Cotton	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Southern EU	0 h	0.6898		13.485	
	24 h	0.2212	0.4555	12.222	12.854
	• 2 d	0.0832	0.3038	11.003	12.233
	• 4 d	0.0761	0.1822	8.9188	11.083
	7 d	0.0468	0.1285	6.5084	9.6151
	14 d	0.0224	0.0808	3.1203	7.1140
	21 d	0.0108	0.0592	1.4960	5.4799
	28 d	0.0052	0.0463	0.7172	4.3750
	42 d	0.0012	0.0318	0.1649	3.0420
	50 d	0.0005	0.0268	0.0712	2.5731
	100 d	0.0000	0.0135	0.0004	1.2933

FOCUS STEP 3 Scenario Cotton	Water body	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
			Actual	TWA	Actual	TWA
D6	ditch	0 h	0.38193		0.930	
		24 h	0.12567	0.21692	0.725	0.895
		2 d	0.03519	0.14484	0.521	0.817
		4 d	0.0062	0.08095	0.308	0.653
		7 d	0.001	0.04755	0.166	0.489
		14 d	<0.001	0.0247	0.052	0.300
		21d	<0.001	0.0168	0.020	0.212
		28 d	<0.001	0.0124	0.008	0.163
		42 d	<0.001	0.0089	0.002	0.110

Application rate

Crop: Tomato / aubergine

Crop interception: no relevance as no runoff or drainage

Number of applications: 2

Interval (d): 10

Application rate(s): 112.5 g as/ha

Application window: no runoff or drainage

FOCUS STEP 2 Scenario tomato/aubergine	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Southern EU	0 h	0.0382		0.2698	
	24 h	0.0126	0.0254	0.2566	0.2632
	2 d	0.0051	0.0171	0.2350	0.2545
	4 d	0.0019	0.0101	0.1918	0.2337
	7 d	0.0012	0.0064	0.1401	0.2042
	14 d	0.0006	0.0037	0.0672	0.1517
	21 d	0.0003	0.0026	0.0322	0.1170

FOCUS STEP 2 Scenario tomato/aubergine	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
	28 d	0.0001	0.0020	0.0154	0.0935
	42 d	0.0000	0.0013	0.0035	0.0650

Metabolite 4'-OH-Pyr Parameters used in FOCUSsw step 1 and 2	Molecular weight: 337.4 g/mol Water solubility (mg/L): 1.4 mg/L Soil or water metabolite: soil and water Koc (L/kg): 2598 L/kg DT_{50} soil (d): 38 days Lab. In accordance with FOCUS SFO) DT50 water/sediment system (d): 15.3 days DT_{50} water (d): 1.2 days DT_{50} sediment (d): 26.8 days Crop interception (%): 50% tomato/aubergine, 75% cotton Maximum occurrence observed: Water/sediment: 15.9% Soil: 6.3% FOCUS STEP 2 (for greenhouse applications a worst case total surface water loading of 0.1% is assumed whereas the default drift value in STEP 2 is 2.38% (therefore the STEP 2 results were divided by 23.8)). Note runoff and drainage input were set at 0, therefore soil DT50 is not utilised in this green house calculation.
Parameters used in FOCUSsw step 3 (if performed)	Not performed
Application rate	Crop: Cotton Crop interception: 75% at step 2 Number of applications: 1 Interval (d): - Application rate(s): 75 g as/ha Application window: June-Sep

FOCUS STEP 1 Scenario Cotton	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
	0h	0.4854		9.620	
	24h	0.3785	0.4319	9.834	9.726
	2d	0.3617	0.4010	9.398	9.671
	4d	0.3304	0.3734	8.541	9.328
	7d	0.2884	0.3458	7.493	8.770
	14d	0.2100	0.2965	5.457	7.596
	21d	0.1530	0.2576	3.974	6.623
	28d	0.1114	0.2260	2.894	5.818
	42d	0.0591	0.1782	1.535	4.593

FOCUS STEP 2 Scenario Cotton	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Southern EU	0 h	0.1151		1.176	
	24 h	0.0531	0.0841	1.123	1.149
	2 d	0.0367	0.0645	1.073	1.124
	4 d	0.0551	0.0516	0.980	1.075
	7 d	0.0413	0.0490	0.856	1.007
	14 d	0.0301	0.0422	0.623	0.870
	21 d	0.0219	0.0367	0.454	0.758
	28 d	0.0160	0.0322	0.331	0.666
	42 d	0.0085	0.0254	0.175	0.526

Application rate	Crop: Tomato / aubergine Crop interception: no relevance as no runoff or drainage Number of applications: 2 Interval (d): 10 Application rate(s): 112.5 g as/ha Application window: no runoff or drainage

FOCUS STEP 2 Scenario tomato/aubergine	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Southern EU	0 h	0.0075		0.0469	
	24 h	0.0040	0.0057	0.0463	0.0466
	2 d	0.0031	0.0047	0.0446	0.0460
	4 d	0.0026	0.0037	0.0408	0.0443
	7 d	0.0023	0.0032	0.0356	0.0417
	14 d	0.0016	0.0025	0.0259	0.0361
	21 d	0.0012	0.0022	0.0189	0.0315
	28 d	0.0009	0.0019	0.0138	0.0277
	42 d	0.0005	0.0015	0.0073	0.0218

Metabolite DPH-Pyr Parameters used in FOCUSsw step 1 and 2	Molecular weight: 245.3 g/mol Soil or water metabolite: water Koc (L/kg): 10 L/kg for water PEC 9620 L/kg for sed PEC DT_{50} soil (d): 1000 days (worst case estimate, no soil DT_{50}) DT50 water/sediment system (d): 4 days DT_{50} water (d): 4 days DT_{50} sediment (d): 1000 days (worst case estimate, no DT_{50}) Crop interception (%): 50% tomato/aubergine, 75% cotton Maximum occurrence observed Soil: 2% (not formed in soil, value is for unidentified radioactivity in extracts) Water/sediment: 12.7% FOCUS STEP 2 (for greenhouse applications a worst case total surface water loading of 0.1% is assumed whereas the default drift value in STEP 2 is 2.38% (therefore the STEP 2 results were divided by 23.8)))). Note runoff and drainage input were set at 0, therefore soil DT50 is not utilised in this green house calculation.
Parameters used in FOCUSsw step 3 (if performed)	Not performed

Application rate	Crop: Cotton Crop interception: 75% at step 2 Number of applications: 1 Interval (d): - Application rate(s): 75 g as/ha Application window: June-Sep

FOCUS STEP 1 Scenario Cotton	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
	0h	0.4534		2.6543	
	24h	0.3805	0.4169	2.6230	2.6386
	2d	0.3200	0.3832	2.2057	2.5235
	4d	0.2263	0.3268	1.5596	2.1937
	7d	0.1345	0.2623	0.9274	1.7748
	14d	0.0400	0.1701	0.2757	1.1560
	21d	0.0119	0.1211	0.0820	0.8239
	28d	0.0035	0.0926	0.0244	0.6298
	42d	0.0003	0.0622	0.0022	0.4229

FOCUS STEP 2 Scenario Cotton	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Southern EU	0 h	0.0661		0.4209	
	24 h	0.0551	0.0606	0.3624	0.3917
	2 d	0.0464	0.0556	0.3048	0.3626
	4 d	0.0619	0.0511	0.2155	0.3104
	7 d	0.0369	0.0499	0.1281	0.2496
	14 d	0.0112	0.0358	0.0381	0.1620
	21 d	0.0034	0.0260	0.0113	0.1154
	28 d	0.0010	0.0200	0.0034	0.0882
	42 d	0.0001	0.0135	0.0003	0.0592

Application rate	Crop: Tomato / aubergine Crop interception: no relevance as no runoff or drainage Number of applications: 2 Interval (d): 10 Application rate(s): 112.5 g as/ha Application window: no runoff or drainage

FOCUS STEP 2 Scenario Tomato/aubergine	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Southern EU	0 h	0.0043		0.0187	
	24 h	0.0036	0.0040	0.0166	0.0177
	2 d	0.0030	0.0037	0.0142	0.0165
	4 d	0.0022	0.0031	0.0101	0.0143
	7 d	0.0013	0.0025	0.0060	0.0116
	14 d	0.0004	0.0016	0.0018	0.0075
	21 d	0.0001	0.0012	0.0005	0.0054
	28 d	0.0000	0.0009	0.0002	0.0041
	42 d	0.0000	0.0006	0.0000	0.0028

Metabolite PYPAC Parameters used in FOCUSsw step 1 and 2	Molecular weight: 167.2 g/mol Water solubility (mg/L): 65000 mg/L (parent value) Soil or water metabolite: soil and water Koc (L/kg): 20.7 L/kg DT_{50} soil (d): 15.7 days DT50 water/sediment system (d): 37.3 days DT_{50} water (d): 21.5 days DT_{50} sediment (d): 27.7 days Crop interception (%): 50% tomato/aubergine, 75% cotton Maximum occurrence observed: Water/sediment: 31.2% Soil: 8.6% FOCUS STEP 2 (for greenhouse applications a worst case total surface water loading of 0.1% is assumed whereas the default drift value in STEP 2 is 2.38% (therefore the STEP 2 results were divided by 23.8)). Note runoff and drainage input were set at 0, therefore soil DT50 is not utilised in this green house calculation.
Parameters used in FOCUSsw step 3 (if performed)	Not performed
Application rate	Crop: Cotton Crop interception: 75% at step 2 Number of applications: 1 Interval (d): - Application rate(s): 75 g as/ha Application window: June-Sep

FOCUS STEP 1 Scenario Cotton	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
	0h	1.2000		0.2252	
	24h	1.1750	1.1875	0.2432	0.2342
	2d	1.1533	1.1758	0.2387	0.2376
	4d	1.1113	1.1540	0.2300	0.2360
	7d	1.0510	1.1226	0.2176	0.2307
	14d	0.9228	1.0541	0.1910	0.2174
	21d	0.8102	0.9912	0.1677	0.2046
	28d	0.7114	0.9333	0.1473	0.1928
	42d	0.5485	0.8310	0.1135	0.1717

FOCUS STEP 2 Scenario Cotton	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Southern EU	0 h	0.1776		0.0359	
	24 h	0.1736	0.1757	0.0353	0.0356
	2 d	0.1704	0.1738	0.0346	0.0353
	4 d	0.1642	0.1705	0.0334	0.0346
	7 d	0.1553	0.1659	0.0315	0.0337
	14 d	0.1363	0.1557	0.0277	0.0316
	21 d	0.1197	0.1464	0.0243	0.0297
	28 d	0.1051	0.1379	0.0214	0.0280
	42 d	0.0810	0.1228	0.0165	0.0249

Application rate	Crop: Tomato / aubergine Crop interception: no relevance as no runoff or drainage Number of applications: 2 Interval (d): 10 Application rate(s): 112.5 g as/ha Application window: no runoff or drainage

FOCUS STEP 2 Scenario Tomato/aubergine	Day after overall maximum	PEC_{SW} (µg/L)		PEC_{SED} (µg/kg)	
		Actual	TWA	Actual	TWA
Southern EU	0 h	0.0110		0.0015	
	24 h	0.0107	0.0109	0.0015	0.0015
	2 d	0.0105	0.0108	0.0014	0.0015
	4 d	0.0102	0.0106	0.0014	0.0014
	7 d	0.0096	0.0103	0.0013	0.0014
	14 d	0.0084	0.0096	0.0011	0.0013
	21 d	0.0074	0.0091	0.0010	0.0012
	28 d	0.0065	0.0085	0.0009	0.0012
	42 d	0.0050	0.0076	0.0007	0.0010

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

Method of calculation and type of study (*e.g.* modelling, field leaching, lysimeter)	For FOCUS gw modelling, values used Modelling using FOCUS model(s), with appropriate FOCUSgw scenarios, according to FOCUS guidance. Model(s) used: FOCUSPEARL 1.1.1 Scenarios (list of names): Thiva and Sevilla Crop: cotton arithm. mean parent DT_{50lab} 8.6 d (normalisation to 10kPa or pF2, 20 °C with Q10 of 2.2). K_{OC}: parent, arithmetic mean 21175, $^1/_n$= 1.15. 4'-OH-Pyr: arithm. mean DT_{50lab} 34.8 d (normalisation to 10kPa or pF2, 20 °C with Q10 of 2.2). K_{OC}: 4'-OH-Pyr, arithmetic mean 2598, $^1/_n$= 0.87. PYPAC: arithm. mean DT_{50lab} 15.7 d (normalisation to 10kPa or pF2, 20 °C with Q10 of 2.2). K_{OC}: PYPAC arithmetic mean 20.7, $^1/_n$= 1.10.

Application rate	Cotton Application rate: 75 g/ha. No. of applications: 1 Time of application (month or season): BBCH 80 before boll opening equated to 75% crop interception Tomato Outdoor FOCUS scenarios used though the GAP pattern is that for use under protection. Application rate: 112.5 g/ha. No. of applications: 2 Time of application (month or season): 13 days then 3 days prior to harvest, BBCH 89 equated to 80% crop interception

PEC(gw) - FOCUS modelling results (80th percentile annual average concentration at 1m)

	Scenario	Parent (µg/L)	Metabolite (µg/L)	
			4'-OH-Pyr	PYPAC
PEARL 1.1.1 Cotton	Sevilla	<0.001	<0.001	<0.001
	Thiva	<0.001	<0.001	<0.001

	Scenario	Parent (µg/L)	Metabolite (µg/L)	
			4'-OH-Pyr	PYPAC
PEARL 1.1.1 tomato/aubergine	Chateaudun	<0.001	<0.001	0.015
	Piacenza	<0.001	<0.001	0.027
	Porto	<0.001	<0.001	0.013
	Sevilla	<0.001	<0.001	0.001
	Thiva	<0.001	<0.001	0.011

SE field use surrogate for NE glasshouse use, Piacenza scenario considered to be conservative enough.

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

Direct photolysis in air ‡	Not studied - no data requested
Quantum yield of direct phototransformation	Φ = 0.08661
Photochemical oxidative degradation in air ‡	Pyriproxyfen: DT_{50} of 6.14 hours derived by the Atkinson model (AOPWIN v1.90). OH (12 h) concentration assumed = $6x10^5$ OH/cm^3 PYPAC: DT_{50} of 0.6 days derived by the Atkinson model (AOPWIN v1.90). OH (24 h) concentration assumed = $9.7x10^6$ OH/cm^3 or 1.97 d OH (12 h) concentration of $6x10^5$ OH/cm^3 is assumed.
Volatilisation ‡	from plant surfaces: no data submitted
	from soil surfaces: no data submitted
Metabolites	-

PEC (air)

Method of calculation	Pyriproxyfen: Expert judgement, based on vapour pressure [<1.33×10^{-5} Pa (at 22.8°C)], dimensionless Henry's Law Constant [<1.16×10^{-25} Pa·m^3·mol^{-1} (at 25°C)], and Atkinson calculation (DT_{50} 0.26 d). PYPAC: Expert judgement, based on calculated vapour pressure [7.77×10^{-2} Pa (at 25°C)], dimensionless Henry's Law Constant [2×10^{-4} Pa·m^3·mol^{-1} (at 25°C)], and Atkinson calculation (DT_{50} 1.97 d).

$PEC_{(a)}$

Maximum concentration	Negligible

Residues requiring further assessment

Environmental occurring metabolite requiring further assessment by other disciplines (toxicology and ecotoxicology) or for which a groundwater exposure assessment is triggerred.	Soil: Pyriproxyfen Surface Water: Pyriproxyfen, 4'-OH-Pyr, DPH-Pyr and PYPAC Sediment: pyriproxyfen, 4'-OH-Pyr, PYPAC Ground water: Pyriproxyfen, 4'-OH-Pyr and PYPAC Air: Pyriproxyfen

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

Soil (indicate location and type of study)	No data provided - none requested
Surface water (indicate location and type of study)	No data provided
Ground water (indicate location and type of study)	No data provided
Air (indicate location and type of study)	No data provided

Points pertinent to the classification and proposed labelling with regard to fate and behaviour data

Not readily biodegradable. Potential for R53

Chapter 2.6 – Effects on Non-target Species

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

Species	Test substance	Time scale	End point (mg/kg bw/day)	End point (mg/kg feed)
Birds ‡				
Bobwhite quail/Mallard duck	a.s. pyriproxyfen	Acute	LD_{50} >1906 mg/kg bw	-
Bobwhite quail	a.s. pyriproxyfen	Short-term	LC50 >863 mg/kg bw/day	>4956 mg/kg feed
Mallard duck	a.s. pyriproxyfen	Long-term	NOEC 70.2 mg/kg bw/day	572 mg/kg feed
Mammals ‡				
Rat	a.s. pyriproxyfen	Acute	LD_{50} >5000 mg/kg bw	-
Rat	a.s. pyriproxyfen	Long-term	NOAEL 13.3 mg/kg bw/day	200 mg/kg feed

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

Crop and application rate:

Tomato and aubergine (T&E), EU S, 2x0.1125 (glasshouse).
Cotton, 1x 0.075.

Indicator species/Category	Time scale	ETE (mg/kg bw/d)	TER[1]	Annex VI Trigger[3]
Tier 1 (Birds)				
Bird: 10 g bw, DWI 2.6 mL/d. Surface water. T&E.	Acute	1.E-05	>2.E+08	10
Herbivorous bird: 300 g bw, DFI 228 g/d. Leafy crops. Cotton.	Acute	5.0	>384	10
Insectivorous bird: 10 g bw, DFI 1.04 g/d. Leafy crops. Cotton.	Acute	4.1	>470	10
Bird: 10 g bw, DWI 2.6 mL/d. Surface water. Cotton.	Acute	4.E-04	>5.E+06	10
Bird: 10 g bw, DWI 2.6 mL/d. Drinking water (puddles and leaf axils). Cotton.	Acute	7.8	>244	10
Herbivorous bird: 300 g bw, DFI 228 g/d. Leafy crops. Cotton.	Short-term	2.3	>379	10

Indicator species/Category	Time scale	ETE (mg/kg bw/d)	TER[1]	Annex VI Trigger[3]
Insectivorous bird: 10 g bw, DFI 1.04 g/d. Leafy crops. Cotton.	Short-term	2.3	>382	10
Herbivorous bird: 300 g bw, DFI 228 g/d. Leafy crops. Cotton.	Long-term		58	5
Insectivorous bird: 10 g bw, DFI 1.04 g/d. Leafy crops. Cotton.	Long-term		31	5
Piscivorous bird 1000 g bw, DFI 206 g/d (fish). T&E.	Long-term		9.E+04	5
Vermivorous bird 100 g bw, DFI 113 g/d (earthworms). Cotton.	Long-term		258	5
Piscivorous bird 1000 g bw, DFI 206 g/d (fish). Cotton.	Long-term		615	5
Tier 1 (Mammals)				
Mammal: 10 g bw, DWI 1.6 mL/d. Surface water. T&E.	Acute	6.E-06	>8E+08	10
Herbivorous mammal: 3000 g bw, DFI 832 g/d. Leafy crops. Cotton.	Acute	1.8	>2763	10
Mammal: 10 g bw, DWI 1.6 mL/d. Surface water. Cotton.	Acute	2.E-04	>2E+07	10
Mammal: 10 g bw, DWI 1.6 mL/d. Drinking water (puddles and leaf axils). Cotton.	Acute	4.8	>1042	10
Herbivorous mammal: 3000 g bw, DFI 832 g/d. Leafy crops. Cotton.	Long-term	0.44	29.9	5
Piscivorous mammal 3000 g bw, DFI 390 g/d (fish). T&E.	Long-term	5.E-04	3E+04	5
Vermivorous mammal 10 g bw, DFI 14 g/d (earthworms). Cotton.	Long-term	0.35	38	5
Piscivorous mammal 3000 g bw, DFI 390 g/d (fish). Cotton.	Long-term	0.07	190	5

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 (Test type(D))	Endpoint	Toxicity (µg a.s./l)
Laboratory tests				
Fish				
Lepomis macrochirus	pyriproxyfen	96 h (f-t)	Mortality, LC_{50}	>270 (A)
Oncorhynchis mykiss	pyriproxyfen	95 d (f-t)	NOEC	4.3 (A)
Oncorhynchus mykiss	S-71639 10EC	96 h (s)	Mortality, LC_{50}	220 (A) (2100 µg form./L)
Oncorhynchus mykiss	4'-OH-Pyr	96 h (f-t)	Mortality, LC_{50}	270 (A)
Oncorhynchus mykiss	PYPAC	96 h (s)	Mortality, LC_{50}	>93000 (A)
Aquatic invertebrates				
Daphnia magna	pyriproxyfen	48 h (f-t)	Immobility, EC_{50}	400 (A)
Daphnia magna	pyriproxyfen	21 d (f-t)	Reproduction, NOEC	0.015 (A)
Mysidopsis bahia	pyriproxyfen	28 d (f-t)	Reproduction, NOEC	0.81 (A)
Daphnia magna	S-71639 10EC	48 h (s)	Immobility, EC_{50}	190 (A) (1800 µg form./L)
Daphnia magna	4'-OH-Pyr	48 h (f-t)	Immobility, EC_{50}	1800 (A)
Daphnia magna	PYPAC	48 h (s)	Immobility, EC_{50}	>95000 (A)
Sediment dwelling organisms				
Chironomus riparius	pyriproxyfen	28 d (s, spiked water)	Emergence, NOEC	10 (B)

Algae				
Selenastrum capricornutum	pyriproxyfen	72 h (s)	Biomass EbC_{50} growth rate ErC_{50}	94 (B) 150 (B)
Selenastrum capricornutum	S-71639 10EC	72 h (s)	Biomass EbC_{50} growth rate ErC_{50}	74 (B) 710 µg form./L) 110 (B) (1100 µg form./L))
Pseudokirchneriella subcapitata	4'-OH-Pyr	72 h (s)	Biomass EbC_{50} growth rate ErC_{50}	>2500 (C) >2500 (C)
Pseudokirchneriella subcapitata	PYPAC	72 h (s)	Biomass EbC_{50} growth rate ErC_{50}	26000 (A) 30000 (A)
Higher plant				
Lemna gibba	pyriproxyfen	14 d (s-s)	Fronds, EC_{50}	>180 (A)
Microcosm or mesocosm tests				
Pyriproxyfen 10EC: NOAEC 5.0 µg a.s./L (B)				

(A) Based on mean measured concentrations.
(B) Based on nominal concentrations (analytically confirmed for initial concentrations).
(C) Based on measured initial concentrations.
(D) f-t = flow through, s = static, s-s = semi=static

Toxicity/exposure ratios for the most sensitive aquatic organism per group for pyriproxyfen (Annex IIIA, point 10.2)

1st Tier

Tomato & aubergine (T&E), 2x0.1125 kg as/ha: distance 1 m; 0.1% drift for greenhouse application and FOCUS Step 2 (no run-off or drainage)
Cotton, 1x0.075 kg as/ha: distance 1 m; FOCUS Step 1 **(**2.77% drift and 10% run-off/drainage)

Crop	Organism	Test substance	Toxicity endpoint (µg a.s./L)	Time-scale	PEC_i (µg a.s./L)	TER	Annex VI Trigger
T&E	*O. mykiss*	product	220	96 h	0.0382	5765	100
Cotton	*O. mykiss*	product	220	96 h	1.5449	142	100
T&E	*O. mykiss*	a.s.	4.3	95 d	0.0382	113	10
Cotton	*O. mykiss*	a.s.	4.3	95 d	1.5449	**2.8**	10
T&E	*Daphnia*	product	190	48 h	0.0382	4979	100

Cotton	*Daphnia*	product	190	48 h	1.5449	123	100
T&E	*Daphnia*	a.s.	0.015	21 d	0.0382	**0.39** (A)	10
Cotton	*Daphnia*	a.s.	0.015	21 d	1.5449	**0.01**	10
T&E	*C.riparius*	a.s.	10	28 d	0.0382	262	10
Cotton	*C.riparius*	a.s.	10	28 d	1.5449	**6.5**	10
T&E	*S. capri-cornutum*	product	74	72 h	0.0382	1939	10
Cotton	*S. capri-cornutum*	product	74	72 h	1.5449	48	10
T&E	*Lemna*	a.s.	>180	14 d	0.0382	>4717	10
Cotton	*Lemna*	a.s.	>180	14 d	1.5449	>117	10

(A)Risk assessment can be done on a weight-of-evidence approach. Considering that the 4th TIER TER of cotton for *Daphnia* is 13 times higher than the trigger and that the PECsw from tomato and aubergine (from FOCUS Step 2) is ten times lower than the PECsw for cotton (from FOCUS Step 3) (0.0382 vs. 0.381 µg a.s./L), there is a safety margin of 130. It is not expected that the effect of the second application in tomato and aubergine is this big. Therefore, the long-term risk for tomato and aubergine should be low.

2nd Tier

Cotton: 1x0.075 kg as/ha: distance 1 m; FOCUS Step 2 (2.77% drift and 3% run-off/drainage)

Crop	Organism	Test substance	Toxicity endpoint (µg a.s./L)	Time-scale	PEC_i (µg a.s./L)	TER	Annex VI Trigger
Cotton	*O. mykiss*	a.s.	4.3	95 d	0.6898	**6.2**	10
Cotton	*Daphnia*	a.s.	0.015	21 d	0.6898	**0.02**	1
Cotton	*C.riparius*	a.s.	10	28 d	0.6898	14	10

3rd Tier

Cotton: 1x0.075 kg as/ha: distance 1.3 m; FOCUS Step 3 (2.77% drift and substance-dependent drainage)

Crop	Organism	Test substance	Toxicity endpoint (µg a.s./L)	Time-scale	PEC_i (µg a.s./L)	TER	Annex VI Trigger
Cotton	*O. mykiss*	a.s.	4.3	95 d	0.381	11	10
Cotton	*Daphnia*	a.s.	0.015	21 d	0.381	**0.04**	10

4th Tier

Cotton: 1x0.075 kg as/ha: distance 1.3 m; FOCUS Step 3 (2.77% drift and substance-dependent drainage)

Crop	Organism	Test substance	Toxicity endpoint (µg a.s./L)	Time-scale	PEC_i (µg a.s./L)	TER	Annex VI Trigger
Cotton	*Daphnia*	a.s.	5	56 d	0.381	13*	**

***** The endpoint is derived from a microcosm only covering zooplankton. The risk to aquatic insects has not been addressed

** The appropriate trigger level should be decide after the risk to aquatic insects has been addressed

Bioconcentration			
	Active substance pyriproxyfen	metabolite DPH-PYR	metabolite PYPAC(C)
$logP_{O/W}$	5.37	3.02(A)	0.97(B)
Bioconcentration factor (BCF)[1] ‡	1379 and 1495 L/kg wwt (radioactivity for PP- and PYR-label, respectively) 660-501 L/kg wwt (active substance)	74(A)	1.4(A)
Annex VI Trigger for the bioconcentration factor	100	-	
Clearance time (days) (CT_{50})	0.86 d (PP-label) and 1.63 d (PYR-label)	-	
(CT_{90})	3.4 d (PP-label) and 8.4 d (PYR-label)	-	

Bioconcentration		
Level and nature of residues (%) in organisms after the 14 day depuration phase	≤ 10.4%	-

[1] only required if log $P_{O/W}$ >3.

(A)Estimated by RMS using Pallas 3.0 (CompuDrug Chemistry Ltd. 1994,95): 3.18

(B) Estimated by RMS according to the formula logBCF=0.85*logPow-0.7

(C) Estimations are made for more metabolites in the DAR, but only the metabolites >10% in water are presented here.

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

Test substance	Acute oral toxicity (LD_{50} µg/bee)	Acute contact toxicity (LD_{50} µg/bee)
a.s. pyriproxyfen	NA	NA
Preparation Pyriproxyfen 10EC	LD50 74 µg a.s./bee	LD50 >100 µg a.s./bee
Field or semi-field tests		
In a field study in Germany (dose rate 1x 75 g a.s./ha), Pyriproxyfen 10% EC did not affect mortality of adults or juvenile stages, overall colony performance or survival and development of eggs and larvae through to adult emergence.		

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

Application rate (g as/ha)	Crop	Route	Hazard quotient	Annex VI Trigger
Laboratory tests				
112.5	Tomato and aubergine	Oral Contact	1.5 <1.1	50 50
75	Cotton	Oral Contact	1.0 <0.75	50 50

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

Laboratory tests with standard sensitive species

Species	Test type, exposure scenario and duration	Test Substance	Dose (g as/ha)	Endpoint	Effect[A]
Aphidius rhopalosiphi	Laboratory, glass, 48 h (mortality), 13 d (fecundity)	Pyriproxyfen 10EC	31.25 62.5 125 250 500	Mortality / mummies per female / reduction of reproduction LR50 ER50	0 / 15 / 35 0 / 17 / 25 13 / 7.0 / 70 63 / n.d.[B] / - 97 / n.d. [B] / - 213 g a.s./ha 81 g a.s./ha
Typhlodromus pyri	Laboratory, glass, 7 d (mortality), 14 d (fecundity)	Pyriproxyfen 10EC	3.75 7.5 15 30 60	Mortality[C] / reproduction / reduction of reproduction LR50 ER50	6.7 / 6.2 / 9 -8.9 / 4.0 / 42 23 / 0.98 / 86 86 / - / - 100 / - / - 20 g a.s./ha 8.1 g a.s./ha

HQ calculations for laboratory tests with standard sensitive species

Crop / species	dose g as/ha	distance (m)	% drift	Exposure (g a.s./ha)	LR50 (g a.s./ha)	ER50 (g a.s./ha)	HQ lethal	HQ sublethal	trigger value[B]
Typhlodromus pyri									
T&E EU N[A]	2 x 30	0	-	51	20	8.1	**2.6**	**6.3**	1
		1	NA	NA	20	8.1	NA	NA	1
T&E EU S[A]	2 x 112.5	0	-	191	20	8.1	**9.6**	**24**	1
		1	NA	NA	20	8.1	NA	NA	1
Cotton EU S	1 x 75	0	-	75	20	8.1	**3.8**	**9.3**	1
		1	2.77	0.21	20	8.1	0.10	0.26	1
Aphidius rhopalosiphi									
T&E EU N[A]	2 x 30	0	-	51	213	81	0.24	0.63	1
		1	NA	NA	213	81	NA	NA	1
T&E EU S[A]	2 x 112.5	0	-	191	213	81	0.90	**2.4**	1
		1	NA	NA	213	81	NA	NA	1
Cotton EU S	1 x 75	0	-	75	213	81	0.35	0.93	1
		1	2.77	0.21	213	81	1E-2	3E-2	1

[A] T&E Tomato & aubergine. EU N and EU S, Northern Europe and Southern Europe, respectively.

[B] ESCORT 2 states that for IGRs a trigger of 50% is used for both lethal and sublethal effects. Hence the risk is considered acceptable if HQ <1 (HQ of 1 is equal to effect of 50%).

Further laboratory and extended laboratory studies

Species	Test type, exposure scenario and duration	Test Substance	Dose (g as/ha)	Endpoint	Effect[A]	Annex VI Trigger
Laboratory tests						
Orius laevigatus	Laboratory, glass, 9 d (mortality), 20 d (fecundity)	Pyriproxyfen 10EC	28.13 56.25 112.5 225 450	Mortality[C] / reproduction / hatching rate / reduction of reproduction LR50, ER50	-5.0 / 17 / 69 / 27 1.7 / 20 / 76 / 5.1 17 / 19 / 79 / 6.3 23 / 27 / 80 / -35 25 / 25 / 72 / -12 >450 g a.s./ha5	30%
Typhlodromus pyri	Extended laboratory[D] 0 d aging	Pyriproxyfen 10EC	75 191.3 225	Mortality[C] / reproduction / reduction of reproduction LR50 ER50	-2.1 / 7.5 / 26 1.1 / 5.6 / 45 6.4 / 4.6 / 55 >225 g a.s./ha 205 g a.s./ha	50%
Typhlodromus pyri	Extended laboratory[D] 7 d aging, 7 d (mortality), 14 d (fecundity)	Pyriproxyfen 10EC	75 191.3 225	Mortality[C] / reproduction / reduction of reproduction LR50, ER50	-10 / 7.7 / 18 0 / 7.5 / 19 -6.9 / 7.7 / 18 >225	50%
Typhlodromus pyri	Extended laboratory[D] 14 d aging	Pyriproxyfen 10EC	75 191.3 225	Mortality[C] / reproduction / reduction of reproduction LR50, ER50	-2.2 / 7.5 / 15 0.5 / 6.4 / 27 6.5 / 7.2 / 18 >225 g a.s./ha	50%
Chrysoperla carnea	Extended laboratory[D] 0 d aging, total duration 34 d	Pyriproxyfen 10EC	75 191.3 225	Mortality[C] / reproduction / hatching rate / reduction of reproduction LR50, ER50	0.4 / 36 / 97 / -2.9 26 / 34 / 88 / 12 37 / 37 / 87 / 4.8 >225 g a.s./ha	50%
Chrysoperla carnea	Extended laboratory[D] 7 d aging, total duration 34 d	Pyriproxyfen 10EC	75 191.3 225	Mortality[C] / reproduction / hatching rate / reduction of reproduction LR50, ER50	13 / 30 / 97 / 13 41 / 30 / 98 / 12 17 / 26 / 91 / 28 >225 g a.s./ha	50%

Species	Test type, exposure scenario and duration	Test Substance	Dose (g as/ha)	Endpoint	Effect(A)	Annex VI Trigger
Chrysoperla carnea	Extended laboratory(D) 14 d aging, total duration 34 d	Pyriproxyfen 10EC	75 191.3 225	Mortality(C) / reproduction / hatching rate / reduction of reproduction LR50, ER50	-3.6 / 26 / 98 / 7.8 22 / 28 / 98 / -1.9 11 / 33 / 96 / -14 >225 g a.s./ha	50%

(A)Effects are adverse effects. Negative percentages therefore imply no adverse effect.
(B)n.d. = not detected.
(C)Corrected mortality according to Abbott formula.
(D)Exposure to residues on field-sprayed potted grape plant leaves with aging.

Field or semi-field tests Not provided

Effects on earthworms, other soil macro-organisms and soil micro-organisms (Annex IIA points 8.4 and 8.5. Annex IIIA, points, 10.6 and 10.7)

Test organism	Test substance	Time scale	End point
Earthworms			
	a.s. pyriproxyfen	Acute 14 days	LC_{50} >1000 mg a.s./kg d.w.soil(A) $LC_{50, corr}$ >500 mg a.s./kg d.w.soil
	a.s. pyriproxyfen	Chronic 8 weeks	not available
Other soil macro-organisms			
Soil mite			not available
Collembola			not available
Soil micro-organisms			
(B)			
Field studies			
not required			

(A) LC50 not corrected for organic content of OECD 207 substrate
(B) Microbial effect studies in original dossier were considered not valid. The applicant did submit a new study which was assessed, accepted and presented in an addendum (December, 2008) by RMS. The studies were not peer reviewed due to Commission regulation 1095/2007.

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

Crop	Application rate (kg as/ha)	Time-scale	Soil PEC (initial)	TER	Annex VI Trigger
Tomato and aubergine	2 x 0.1125	Acute	0.055	9091	10
Cotton	0.075	Acute	0.060	8333	10

Effects on non target plants (Annex IIA, point 8.6, Annex IIIA, point 10.8)

Preliminary screening data

Initial screening data showed effects <50% in barnyard grass, oat, velvetleaf and radish at 8000 g a.s./ha.

Effects on other non-target organisms (Annex IIA, point 8.6, Annex IIIA, point 10.8)

Initial screening data showed no insecticidal or fungicidal activity.

Effects on biological methods for sewage treatment (Annex IIA, point 8.7)

Respiratory rate activated sludge — pyriproxyfen: EC_{50} >100 mg a.s./L

Ecotoxicologically relevant compounds (consider parent and all relevant metabolites requiring further assessment from the fate section)

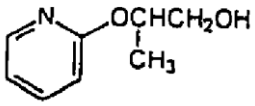
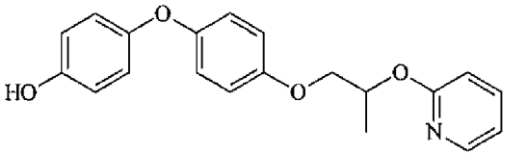
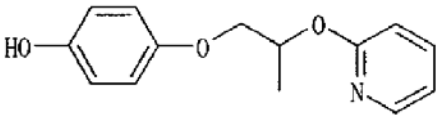
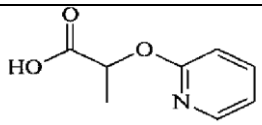
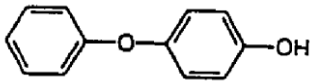
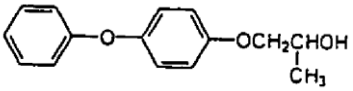
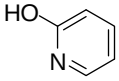
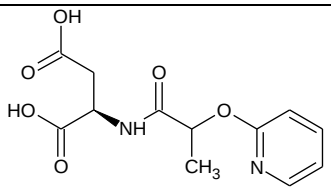
Compartment	
soil	Pyriproxyfen
water	At least pyriproxyfen but data gaps would need to be filled before DPH-pyr could be excluded from the monitoring definition.
sediment	Pyriproxyfen
groundwater	Pyriproxyfen

Classification and proposed labelling with regard to ecotoxicological data (Annex IIA, point 10 and Annex IIIA, point 12.3)

	RMS/peer review proposal
Active substance pyriproxyfen	Symbol : N Risk phrase : R50, R53 Safety phrase : S60, S61

	RMS/peer review proposal
Preparation Pyriproxyfen 10EC	Symbol : N Risk phrase : R50, R53 Safety phrase : S60, S61

APPENDIX B – USED COMPOUND CODE(S)

Code/Trivial name*	Chemical name	Structural formula
PYPA	(RS)-2-(2-pyridyloxy)propyl alcohol	
4'-OH-pyr	4-(4'-hydroxyphenoxyphenyl) (RS)-2-(2-pryidyloxy)propyl ether	
DPH-pyr	4-hydroxyphenyl (RS)-2-(2-pyridyloxy)propyl ether	
PYPAC	(RS)-2-(2-pyridyloxy)propionic acid	
POP	4-phenoxyphenol	
POPA	(RS)-2-hydroxypropyl 4-phenoxyphenyl ether	
2-OH-PY	2-hydroxypyridin	
PYPAC-Asp aspartic acid amide of (RS)-2-(2-pyridyloxy)propionic acid	N-[(RS)-2-(2-pyridyloxy)propionyl]-(S)-aspartic acid	

* The metabolite name in bold is the name used in the conclusion.

ABBREVIATIONS

1/n	slope of Freundlich isotherm
ε	decadic molar extinction coefficient
°C	degree Celsius (centigrade)
µg	microgram
µm	micrometer (micron)
a.s.	active substance
AChE	acetylcholinesterase
ADE	actual dermal exposure
ADI	acceptable daily intake
AF	assessment factor
AOEL	acceptable operator exposure level
AP	alkaline phosphatase
AR	applied radioactivity
ARfD	acute reference dose
AST	aspartate aminotransferase (SGOT)
AV	avoidance factor
BCF	bioconcentration factor
BUN	blood urea nitrogen
bw	body weight
CAS	Chemical Abstract Service
CFU	colony forming units
ChE	cholinesterase
CI	confidence interval
CIPAC	Collaborative International Pesticide Analytical Council Limited
CL	confidence limits
d	day
DAA	days after application
DAR	draft assessment report
DAT	days after treatment
DM	dry matter
DT_{50}	period required for 50 percent disappearance (define method of estimation)
DT_{90}	period required for 90 percent disappearance (define method of estimation)
dw	dry weight
EbC_{50}	effective concentration (biomass)
EC_{50}	effective concentration
ECHA	European Chemical Agency
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELF	early life stage
ELINCS	European List of New Chemical Substances
EMDI	estimated maximum daily intake
ER_{50}	emergence rate/effective rate, median
ErC_{50}	effective concentration (growth rate)
EU	European Union

EUROPOEM	European Predictive Operator Exposure Model
f(twa)	time weighted average factor
FAO	Food and Agriculture Organisation of the United Nations
FIR	Food intake rate
FOB	functional observation battery
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
g	gram
GAP	good agricultural practice
GC	gas chromatography
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GGT	gamma glutamyl transferase
GM	geometric mean
GS	growth stage
GSH	glutathion
h	hour(s)
ha	hectare
Hb	haemoglobin
Hct	haematocrit
hL	hectolitre
HPLC	high pressure liquid chromatography or high performance liquid chromatography
HPLC-MS	high pressure liquid chromatography – mass spectrometry
HQ	hazard quotient
IEDI	international estimated daily intake
IESTI	international estimated short-term intake
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint Meeting on the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
K_{doc}	organic carbon linear adsorption coefficient
kg	kilogram
K_{Foc}	Freundlich organic carbon adsorption coefficient
L	litre
LC	liquid chromatography
LC_{50}	lethal concentration, median
LC-MS	liquid chromatography-mass spectrometry
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LD_{50}	lethal dose, median; dosis letalis media
LDH	lactate dehydrogenase
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification (determination)
m	metre
M/L	mixing and loading
MAF	multiple application factor
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume

mg	milligram
mL	millilitre
mm	millimetre
MRL	maximum residue limit or level
MS	mass spectrometry
MSDS	material safety data sheet
MTD	maximum tolerated dose
MWHC	maximum water holding capacity
NESTI	national estimated short-term intake
ng	nanogram
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
OM	organic matter content
Pa	Pascal
PD	proportion of different food types
PEC	predicted environmental concentration
PEC_{air}	predicted environmental concentration in air
PEC_{gw}	predicted environmental concentration in ground water
PEC_{sed}	predicted environmental concentration in sediment
PEC_{soil}	predicted environmental concentration in soil
PEC_{sw}	predicted environmental concentration in surface water
pH	pH-value
PHED	pesticide handler's exposure data
PHI	pre-harvest interval
PIE	potential inhalation exposure
pK_a	negative logarithm (to the base 10) of the dissociation constant
P_{ow}	partition coefficient between *n*-octanol and water
PPE	personal protective equipment
ppm	parts per million (10^{-6})
ppp	plant protection product
PT	proportion of diet obtained in the treated area
PTT	partial thromboplastin time
QSAR	quantitative structure-activity relationship
r^2	coefficient of determination
RPE	respiratory protective equipment
RUD	residue per unit dose
SC	suspension concentrate
SD	standard deviation
SFO	single first-order
SSD	species sensitivity distribution
STMR	supervised trials median residue
$t_{1/2}$	half-life (define method of estimation)
TER	toxicity exposure ratio
TER_A	toxicity exposure ratio for acute exposure
TER_{LT}	toxicity exposure ratio following chronic exposure
TER_{ST}	toxicity exposure ratio following repeated exposure
TK	technical concentrate

TLV	threshold limit value
TMDI	theoretical maximum daily intake
TRR	total radioactive residue
TSH	thyroid stimulating hormone (thyrotropin)
TWA	time weighted average
UDS	unscheduled DNA synthesis
UV	ultraviolet
W/S	water/sediment
w/v	weight per volume
w/w	weight per weight
WBC	white blood cell
WG	water dispersible granule
WHO	World Health Organisation
wk	week
yr	year