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Peer review of the pesticide risk assessment of the active substance pyriproxyfen

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Abstract

The conclusions of EFSA following the peer review of the initial risk assessments carried out by the competent authorities of the rapporteur Member State the Netherlands and co-rapporteur Member State Spain for the pesticide active substance pyriproxyfen and the assessment of applications for maximum residue levels (MRLs) are reported. The context of the peer review was that required by Commission Implementing Regulation (EU) No 844/2012. The conclusions were reached on the basis of the evaluation of the representative uses of pyriproxyfen as an insecticide on citrus fruit, pome fruit (apple, pears), tomatoes, ornamentals (field use) and tomatoes, ornamentals (greenhouse application). MRLs were assessed in citrus fruits. The reliable end points, appropriate for use in regulatory risk assessment and the proposed MRLs, are presented. Missing information identified as being required by the regulatory framework is listed. Concerns are identified.

Keywords: pyriproxyfen, peer review, risk assessment, pesticide, insecticide

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Amendment: Some mistyping errors were corrected in Table 5 on page 20 of the conclusion. To avoid confusion, the older version of the output has been removed from the EFSA Journal, but is available on request, as is a version showing all the changes made.

Update: This scientific output, approved on 17 May 2019, supersedes the previous output published on 6 August 2009 (EFSA, 2009).

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Summary

Commission Implementing Regulation (EU) No 844/2012, as amended by Commission Implementing Regulation (EU) No 2018/1659, lays down the procedure for the renewal of the approval of active substances submitted under Article 14 of Regulation (EC) No 1107/2009. The list of those substances is established in Commission Implementing Regulation (EU) No 686/2012. Pyriproxyfen is one of the active substances listed in Regulation (EU) No 686/2012.

In accordance with Article 1 of Regulation (EU) No 844/2012, the rapporteur Member State (RMS), the Netherlands, and co-rapporteur Member State (co-RMS), Spain, received an application from Sumitomo Chemical Agro Europe for the renewal of approval of the active substance pyriproxyfen. In addition, Sumitomo Chemical Agro Europe submitted applications for maximum residue levels (MRLs), as referred to in Article 7 of Regulation (EC) No 396/2005.

An initial evaluation of the dossier on pyriproxyfen was provided by the RMS in the renewal assessment report (RAR), and subsequently, a peer review of the pesticide risk assessment on the RMS evaluation was conducted by EFSA in accordance with Article 13 of Commission Implementing Regulation (EU) No 844/2012, as amended by Commission Implementing Regulation (EU) No 2018/1659. The following conclusions are derived.

The use of pyriproxyfen according to the representative uses as an insecticide on citrus and pome fruits, tomatoes and ornamentals, as proposed at the European Union (EU) level result in a sufficient insecticidal efficacy against the target organisms.

In the area of mammalian toxicology, the reliability of most of the available studies could not be concluded upon since validated analytical methods were not provided and this led to issues that could not be finalised. Differences in the metabolism of pyriproxyfen in the different animal species and in humans could not be excluded based on the available data (issue that could not be finalised).

In the area of residues, the consumer dietary risk assessment cannot be finalised in view of the identified data gaps. Due to the large margin of safety observed in the consumer dietary intake calculation, it can reasonably be assumed that the potential complete degradation of the racemic mixture to a potentially more toxic enantiomer in plant matrices will have a negligible impact on the consumer toxicological burden.

An MRL application has been submitted to modify the current EU MRL on citrus fruit. Sufficient and acceptable residue trials were submitted to derive an MRL for citrus fruit. As the intended use on citrus fruit was the same as the representative use, the use in this MRL application does not trigger a revision of the calculated livestock dietary burden and the consumer dietary risk assessment.

The data available on environmental fate and behaviour were sufficient to carry out the required environmental exposure assessments at the EU level for the representative uses, with the notable exception that the consumer risk assessment from the consumption of drinking water could not be finalised for all the representative uses since information on the effect of water treatment processes on the nature of residues of both the active substance and its identified metabolites potentially present in surface, when surface water is abstracted for drinking water was insufficient.

In the area of ecotoxicology, high chronic risk to fish at FOCUS Step 4 was concluded for the field uses in ornamentals, citrus and pome fruit (early and late). High chronic risk for fish, for aquatic invertebrates and for sediment-dwelling organisms (exposure via surface water) could not be excluded for the greenhouse soilless uses in ornamentals and for the walk-in tunnels (issue that could not be finalised). A low risk to sediment-dwelling organisms could not be concluded for the exposure via the sediment. High acute risk to aquatic invertebrates and to algae was also indicated for walk-in tunnels. Satisfactory information was not provided to address the preferential transformation of the enantiomers of pyriproxyfen and metabolites 4′-OH-Pyr, PYPAC and DPH-Pyr, which contain chiral carbon atom. Due to the insufficient margin of safety between hazard endpoints and predicted environmental concentrations (PEC) in the available environmental risk assessments, the chronic risk assessment to aquatic invertebrates for metabolite PYPAC could not been finalised.

The risk to honeybees from the field use in ornamentals and the risk from sublethal effects for all field uses could not be concluded upon.

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Background

Commission Implementing Regulation (EU) No 844/2012 as amended by Commission Implementing Regulation (EU) No 2018/1659[1], (hereinafter referred to as 'the Regulation'), lays down the provisions for the procedure of the renewal of the approval of active substances, submitted under Article 14 of Regulation (EC) No 1107/2009[2]. This regulates for the European Food Safety Authority (EFSA) the procedure for organising the consultation of Member States, the applicant(s) and the public on the initial evaluation provided by the rapporteur Member State (RMS) and/or co-rapporteur Member State (co-RMS) in the renewal assessment report (RAR), and the organisation of an expert consultation where appropriate.

In accordance with Article 13 of the Regulation, unless formally informed by the European Commission that a conclusion is not necessary, EFSA is required to adopt a conclusion on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009 within 5 months from the end of the period provided for the submission of written comments, subject to an extension of up to 8 months where additional information is required to be submitted by the applicant(s) in accordance with Article 13(3).

In accordance with Article 1 of the Regulation, the RMS the Netherlands and co-RMS Spain received an application from Sumitomo Chemical Agro Europe for the renewal of approval of the active substance pyriproxyfen. In addition, Sumitomo Chemical Agro Europe submitted application for maximum residue levels (MRLs) as referred to in Article 7 of Regulation (EC) No 396/2005[3]. Complying with Article 8 of the Regulation, the RMS checked the completeness of the dossier and informed the applicant, the co-RMS (Spain), the European Commission and EFSA about the admissibility.

The RMS provided its initial evaluation of the dossier on pyriproxyfen in the RAR, which was received by EFSA on 14 December 2017 (Netherlands, 2017). The RAR included a proposal to set MRLs, submitted under Article 7 of Regulation (EC) No 396/2005.

In accordance with Article 12 of the Regulation, EFSA distributed the RAR to the Member States and the applicant, Sumitomo Chemical Agro Europe, for consultation and comments on 8 May 2018. EFSA also provided comments. In addition, EFSA conducted a public consultation on the RAR. EFSA collated and forwarded all comments received to the European Commission on 10 July 2018. At the same time, the collated comments were forwarded to the RMS for compilation and evaluation in the format of a reporting table. The applicant was invited to respond to the comments in column 3 of the reporting table. The comments and the applicant's response were evaluated by the RMS in column 3.

The need for expert consultation and the necessity for additional information to be submitted by the applicant in accordance with Article 13(3) of the Regulation were considered in a telephone conference between EFSA and the RMS on 24 August 2018. On the basis of the comments received, the applicant's response to the comments and the RMS's evaluation thereof, it was concluded that additional information should be requested from the applicant, and that EFSA should conduct an expert consultation in the areas of mammalian toxicology, environmental fate and behaviour and ecotoxicology.

The outcome of the telephone conference, together with EFSA's further consideration of the comments, is reflected in the conclusions set out in column 4 of the reporting table. All points that were identified as unresolved at the end of the comment evaluation phase and which required further consideration, including those issues to be considered in an expert consultation, were compiled by EFSA in the format of an evaluation table.

The conclusions arising from the consideration by EFSA, and as appropriate by the RMS, of the points identified in the evaluation table, together with the outcome of the expert consultation and the written consultation on the assessment of additional information, where these took place, were reported in the final column of the evaluation table.

A final consultation on the conclusions arising from the peer review of the risk assessment and on the proposed MRLs took place with Member States via a written procedure in April–May 2019.

This conclusion report summarises the outcome of the peer review of the risk assessment of the active substance and the representative formulation, evaluated on the basis of the representative uses

[1] Commission Implementing Regulation (EU) 2018/1659 of 7 November 2018 amending Implementing Regulation (EU) No 844/2012 in view of the scientific criteria for the determination of endocrine disrupting properties introduced by Regulation (EU) 2018/605. OJ L 278, 8.11.2018, p. 3–6.

[2] Regulation (EC) No 1107/2009 of 21 October 2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p. 1–50.

[3] Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC. OJ L 70, 16.3.2005, p. 1–16.

of pyriproxyfen as an insecticide on citrus fruit, pome fruit (apple, pears), tomatoes, ornamentals (field use) and tomatoes, ornamentals (greenhouse application), as proposed by the applicant. In accordance with Article 12(2) of Regulation (EC) No 1107/2009, risk mitigation options identified in the RAR and considered during the peer review are presented in the conclusion. MRLs were assessed in citrus fruit. A list of the relevant end points for the active substance and the formulation and the proposed MRLs is provided in Appendix A.

In addition, a key supporting document to this conclusion is the peer review report (EFSA, 2019), which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the initial commenting phase to the conclusion. The peer review report comprises the following documents, in which all views expressed during the course of the peer review, including minority views, where applicable, can be found:

- the comments received on the RAR;
- the reporting table (24 August 2018);
- the evaluation table (16 May 2019);
- the reports of the scientific consultation with Member State experts (where relevant);
- the comments received on the assessment of the additional information (where relevant);
- the comments received on the draft EFSA conclusion.

Given the importance of the RAR, including its revisions (Netherlands, 2019), and the peer review report, both documents are considered as background documents to this conclusion and thus are made publicly available.

It is recommended that this conclusion report and its background documents would not be accepted to support any registration outside the European Union (EU) for which the applicant has not demonstrated that it has regulatory access to the information on which this conclusion report is based.

The active substance and the formulated product

Pyriproxyfen is the ISO common name for 4-phenoxyphenyl (*RS*)-2-(2-pyridyloxy)propyl ether (IUPAC), only produced as a racemate. Pyriproxyfen is an insect growth regulator (IGR).

The representative formulated product for the evaluation was 'Pyriproxyfen 100 g/L EC', an emulsifiable concentrate (EC) containing 100 g/L pyriproxyfen.

The representative uses evaluated were foliar spray applications for control of scales in citrus and pome fruits and against white fly in tomatoes and ornamentals. Full details of the Good Agricultural Practices (GAPs) can be found in the list of end points in Appendix A.

Data were submitted to conclude that the use of pyriproxyfen according to the representative uses proposed at EU level results in a sufficient insecticidal efficacy against the target organisms, following the guidance document SANCO/2012/11251-rev. 4 (European Commission, 2014b).

Satisfactory information was not provided to address the preferential transformation of the enantiomers of pyriproxyfen and metabolites 4'-OH-Pyr, PYPAC and DPH-Pyr, which contain chiral carbon atom. Considering the high margin of safety this would not trigger a concern in mammalian toxicology, in residues and in soil compartment assessment for the representative uses evaluated. However, for the chronic risk assessment to aquatic invertebrates for metabolite PYPAC and the acute risk assessment to fish for metabolite 4'-OH-Pyr, this data gap resulted in an assessment not finalised due to the insufficient margin of safety between hazard endpoints and predicted environmental concentrations (PEC) indicated in the available environmental risk assessments.

Conclusions of the evaluation

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

The following guidance documents were followed in the production of this conclusion: European Commission (2000a,b, 2010a).

The proposed specification for pyriproxyfen is based on batch data from industrial plant production. The minimum purity of the technical material is 970 g/kg. Toluene is considered as a relevant impurity with a maximum content of 5 g/kg. The manufactured technical material meets the requirements of the existing FAO specification in terms of minimum purity and relevant impurities are not mentioned in FAO specification (715/TC, October 2017 belonging to Sumitomo Chemical Co. Ltd, Tagros Chemicals

India Limited and Rudong Zhongyi Chemical Co., Ltd.). The batches used in the (eco)toxicological assessment support the proposed new specification (see Sections 2 and 5). It should be noted that based on the data for the renewal higher minimum purity for the active substance could be set and lower levels for some of the significant impurities could be defined. Toluene is proposed as a relevant impurity therefore it is proposed that an update of the reference specification would be needed since in the current reference specification no relevant impurities are specified.

The main data regarding the identity of pyriproxyfen and its physical and chemical properties are given in Appendix A. The following data gaps related with the physical, chemical and technical properties of the representative formulation were identified: surface tension studied at highest use-in concentration and an accelerated storage stability study.

Adequate methods are available for the generation of data required for the risk assessment except for the (old) toxicological studies, for which no information was submitted (data gap). Methods of analysis are available for the determination of the active substance and the relevant impurity in the technical material and in the representative formulations and for the determination of the respective impurities in the technical material. It should be noted that there are CIPAC methods for determination of the active substance in the technical material (CIPAC 715/TC/M/-) and in the formulation (CIPAC 715/EC/M/-).

Pyriproxyfen residues can be monitored in food and feed of plant origin by the QuEChERS method using high-performance liquid chromatography with tandem mass spectrometry (HPLC–MS/MS) with a limit of quantification (LOQ) of 0.01 mg/kg in the four major crop groups and black tea. However, it should be noted that the extraction procedure used was verified for high water and high acid content matrices but not for dry and high oil content matrices (data gap). Pyriproxyfen residues in food of animal origin can be determined by the QuEChERS method using liquid chromatography with tandem mass spectrometry (LC–MS/MS) with LOQ of 0.01 mg/kg in all animal matrices. It should be noted that the extraction efficiency was not verified in milk. However, it should be noted that MRLs for animal products were not set and therefore a monitoring method is not required.

Pyriproxyfen residues in soil and air can be monitored by gas chromatography with nitrogen–phosphorus detector (GC-NPD) with LOQs of 0.01 mg/kg and 1 μg/m^3, respectively. Pyriproxyfen residues in surface water can be analysed by QuEChERS LC–MS/MS with a LOQ of 0.001 μg/L and in drinking water by gas chromatography with mass spectrometry (GC–MS) with a LOQ of 0.1 μg/L.

Pyriproxyfen residues in body tissues can be determined by using the monitoring method for residue in food of animal origin. Analytical method for monitoring of pyriproxyfen residues in body fluids was not provided (data gap).

2. Mammalian toxicity

The following guidance documents were followed in the production of this conclusion: European Commission (2003, 2012), EFSA PPR Panel (2012), EFSA (2014b) and ECHA (2017). Pyriproxyfen was discussed in the Pesticide Peer Review meeting 190 in February 2019.

As concerns the literature review in accordance with EFSA (2011), the exclusion of articles after the full-text assessment should be further justified (with the support of more detailed assessment of the full-text articles) (data gap).

The **technical specification** is supported by the batches used in critical toxicological studies. Toluene was identified as a toxicologically relevant impurity with a maximum acceptable level of 5 g/kg. The other impurities were concluded as not toxicologically relevant, based on available data including quantitative structure–activity relationship (QSAR) analyses and read-across considerations. The reliability of the (old) toxicological studies cannot be concluded since validated analytical methods have not been demonstrated (issue not finalised, see also Section 1).

Pyriproxyfen is an isomeric mixture, only produced as a racemate. The toxicological studies were performed with the racemic mixture and no specific toxicological data were provided for the individual isomers nor requested.

Pyriproxyfen showed a limited absorption value after oral administration in rats (40% based on bile and urine excretion). Mainly excreted in faeces but also in urine, the compound showed the highest concentrations in the liver, fat, kidney and blood, showing a potential for bioaccumulation. Although it was extensively metabolised in rats, no major metabolite (> 10%) was identified in urine or bile; whereas in mice, 4'-OH-pyriproxyfen glucuronide was found to be a major metabolite in urine (> 10% of AR, only at high dose of 1,000 mg/kg bw). Based on the available data in rats, where only minor metabolites have been identified in body fluids and tissues, the residue definition for body fluids and tissues includes only

pyriproxyfen. No experimental data were provided for the comparative *in vitro* metabolism with other species, including human cell systems (data gap and issue that could not be finalised).

Pyriproxyfen exhibited a low **acute toxicity** when administered orally, dermally or by inhalation in rats or mice. It is neither a skin nor eye irritant and is unlikely to be a skin sensitiser. Pyriproxyfen did not demonstrate phototoxic potential *in vitro*. Considering that the maximal UV absorption was below 310 nm of wavelength, a data gap is set for additional phototoxicity (and photogenotoxicity) assessment below 310 nm (acknowledging that there is currently no OECD guideline for testing phototoxicity with UVB wavelengths).

In **short-term** dietary studies, the main target organ in all species was the liver. For the rat studies (28-day, 90-day and 6-month), the lowest no observed adverse effect level (NOAEL) was 23.5 mg/kg body weight (bw) per day. For the dog studies (28-day, 90-day and two 1-year studies), the overall NOAEL is 10 mg/kg bw per day from the second 1-year study, based on liver toxicity (increased weight, changes in clinical chemistry parameters and histopathological findings). In a 21-day dermal study with rats, no local or systemic effects were observed up to the highest dose tested. In a 28-day inhalation study with rats, the NOAEL was 86.8 mg/kg bw per day based on salivation, reduced body weight gain, increased lactate dehydrogenase (LDH) and changes in organ weights (liver, spleen and lung).

Based on available **genotoxicity** studies (*in vitro* and *in vivo*), it was concluded that pyriproxyfen is not genotoxic.

In the **long-term** toxicity study with rats, the systemic NOAEL was 27.2 mg/kg bw per day based on body weight and liver changes (weight, clinical chemistry and histopathology), whereas the carcinogenic NOAEL was 138 mg/kg bw per day (high dose level). For the 78-week mouse study, the systemic lowest observable adverse effect level (LOAEL) is 16.4 mg/kg bw per day (low dose) based on reduced survival rate observed at all doses. Increased liver weight, increased severity of systemic amyloidosis and histopathological changes in the kidneys were also observed at the mid- and high doses. The carcinogenic NOAEL is 107.3 mg/kg bw per day based on liver haemangiosarcoma. The experts considered this finding as an equivocal evidence of carcinogenic potential, not sufficient to propose classification. It was concluded that pyriproxyfen was unlikely to be carcinogenic.[4]

In **reproductive toxicity** studies with rats, fertility and overall reproductive performance were not impaired. The relevant parental NOAEL was 13.3 mg/kg bw per day, while the offspring NOAEL was 66.7 mg/kg bw per day based on decreased body weight. With regard to the second combined developmental and reproductive toxicity study with rats, the experts agreed with a maternal NOAEL of 100 mg/kg bw per day while the developmental NOAEL was agreed at 30 mg/kg bw per day based on increased ambulation in an open field test with male pups. The RMS disagreed with the developmental NOAEL as agreed during the meeting.[5] For the rat developmental toxicity, a maternal NOAEL of 100 mg/kg bw per day was identified while the developmental LOAEL was 100 mg/kg bw per day based on an increased incidence of opening of the foramen transversarium of the 7th cervical vertebra (skeletal variation).[5] For the rabbit developmental toxicity, the maternal NOAEL was 100 mg/kg bw per day based on increased abortions and/or premature deliveries. The developmental NOAEL was 100 mg/kg bw per day based on increased incidences of visceral malformations at 300 mg/kg bw per day, not reproducible at the high dose (1,000 mg/kg bw per day) since an insufficient number of dams was present for evaluation. The experts concluded that pyriproxyfen was unlikely to be teratogenic.[6]

With regard to the available **neurotoxicity** studies with rats, the acute neurotoxic NOAEL was 300 mg/kg bw based on decreased total and ambulatory motor activity counts (in males) while the 90-day neurotoxic NOAEL was 1,111 mg/kg bw per day (high dose tested). Based on the regulatory studies submitted for pyriproxyfen together with the publications from the literature review where a link of pyriproxyfen to microcephaly was reported, the experts agreed that there was no indication of a link between the active substance and the finding of microcephaly.

In a 28-day mouse **immunotoxicity** study with pyriproxyfen, adverse effects on the immune function were not observed.

With regard to the assessment of the endocrine-disrupting (**ED**) potential of pyriproxyfen according to the ECHA/EFSA guidance (2018), the Oestrogen, androgen, thyroid or steroidogenic (EATS)-mediated parameters were considered as not being sufficiently investigated in routine toxicological studies where evidence of EATS-mediated adverse effects was not observed. In addition, several specific ED studies *in vitro* and *in vivo* demonstrated negative results or indirect effects mediated by liver enzyme induction

[4] Refer to experts' consultation 2.3 in the Report of Pesticides Peer Review Experts' Meeting 190 (EFSA, 2019).
[5] Refer to experts' consultation 2.4 in the Report of Pesticides Peer Review Experts' Meeting 190 (EFSA, 2019).
[6] Refer to experts' consultation 2.5 in the Report of Pesticides Peer Review Experts' Meeting 190 (EFSA, 2019).

or secondary to decreased body weight. According to point 3.6.5 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, it can be concluded that pyriproxyfen is not an endocrine disruptor.[7]

For the **metabolite** PYPAC, a low acute oral toxicity was observed, and negative results were obtained in *in vitro* genotoxicity studies. Information on its repeat-dose toxicity was not available. For the metabolites 4'-OH-Pyr (and conjugate), 2,5-OH-PY, POPA and POP sulfate conjugate and PYPA, since none of them can be considered as a major rat metabolite (systemically available), they are not covered by the toxicological studies with pyriproxyfen. However, taking into account the results of the QSAR analysis, a genotoxic potential can be excluded for all these metabolites (see also Section 3).

During the first peer review (European Commission, 2010b), an acceptable daily intake (**ADI**) of 0.1 mg/kg bw per day was set based on the NOAEL of 10 mg/kg bw per day in the 1-year dog study, applying an uncertainty factor (UF) of 100. For the renewal, the agreed ADI is 0.05 mg/kg bw per day based on the 78-week mouse study and applying an increased UF of 300 for using a LOAEL instead of a NOAEL. For the renewal, the agreed acute reference dose (**ARfD**) is 1 mg/kg bw based on an increased incidence of malformations in the developmental rabbit study, applying an UF of 100 while in the first peer review, the derivation of an **ARfD** was not considered necessary. For the acceptable operator exposure level (**AOEL**), the original value of 0.04 mg/kg bw per day has been confirmed, based on the 1-year dog study. The acute acceptable operator exposure level (**AAOEL**) was agreed at 0.4 mg/kg bw per day, based on increased incidence of malformations in the developmental rabbit study. Both AOEL and AAOEL have been derived with the application of an UF of 100 and a correction for an oral absorption value of 40%.

Using the triple pack approach (combination of *in vitro* and *in vivo* results with pyriproxyfen 100 g/L EC, following the EFSA PPR Panel, 2012), the dermal absorption values were 3% for the concentrate and 4% for the dilution.

For operators, the **exposure** estimates were below the AOEL/AAOEL without the use of personal protective equipment (PPE) for outdoor (EFSA model) and indoor (Dutch greenhouse model) uses. Similarly, no concern was raised for residents and bystanders exposed during upward and downward spraying using the EFSA model. Finally, for the workers performing harvesting activities in the different crops, no PPE was required according to the EFSA model.

It is noted that the relative toxicity and possible preferential metabolism of the enantiomers was not investigated, however, considering the high margin between worker and bystander exposure and the AOEL/AAOEL, it is considered unlikely that the reference values would be exceeded even if a complete shift would occur after application to a potentially more toxic enantiomer. The RMS considered unlikely that a significant change in isomeric composition would occur.

3. Residues

The assessment in the residue section is based on the following documents: OECD (2009, 2011), European Commission (2011), JMPR (2004, 2007).

3.1. Representative use residues

The metabolism of pyriproxyfen in primary crops was investigated upon foliar application on fruit (apples, tomatoes, cucumbers, oranges) and on pulses/oilseeds (cotton) crop groups using phenoxyphenyl-^{14}C label and pyridyl-^{14}C label of pyriproxyfen, respectively. Pyriproxyfen was predominant in apples, tomatoes and oranges (45–68% total radioactive residue (TRR)) and the metabolites 4'-OH-PYR free in apples at 11% TRR (0.021 mg eq/kg) and PYPA (free and conjugated) in tomatoes at 11% TRR (0.03 mg eq/kg) were also recovered. All other identified metabolites were present as very minor compounds (< 10% TRR or < 0.01 mg eq/kg). The metabolism study on cucumbers with direct application to the surface of the leaves and fruits can be considered as supportive data and showed a similar metabolic pattern, besides the parent compound (up to 38% TRR), 4'-OH-PYR (free and conjugated) and POPA compounds accounted for maximum 17% TRR and 11.5% TRR, respectively, in cucumber fruit. In cotton seed and gin trash, pyriproxyfen was found at ca. 4% of TRR and up to 43% TRR, respectively, and a significant part of the radioactive residues was shown to be incorporated into natural plant constituents in cotton seed (71–81% TRR) and in cotton gin trash (12–17% TRR). All other components of the residue were below 10% TRR. All the metabolites identified at a level > 10% TRR were concluded to be not genotoxic (see Section 2). Since

[7] Refer to experts' consultation 2.6 in the Report of Pesticides Peer Review Experts' Meeting 190 (EFSA, 2019).

the parent pyriproxyfen was the major compound of the total residues in all crops, the residue definition for **monitoring** and **risk assessment** is proposed as pyriproxyfen only for fruit and pulses/oilseeds crops following foliar treatment.

Having regard to the low to moderate persistence of pyriproxyfen in soil (laboratory DT_{90}: 11–135 days), rotational crops metabolism studies are triggered. In a confined rotational crop metabolism study (0.9N), radish, lettuce and wheat were planted at 30-day plant-back intervals (PBIs). The total radioactive residues were < 0.01 mg eq/kg in lettuce and radish root, 0.011 mg eq/kg in radish leaves and wheat forage and accounted for up to 0.081 mg eq/kg in wheat grain, 0.059 mg eq/kg in wheat straw and 0.082 mg eq/kg in wheat chaff. In wheat grain, the major part of the radioactive residues was found to be incorporated into natural plant constituents (up to 88% TRR) while in wheat straw, the extracted radioactive residues were constituted of unidentified compounds, each below 10% TRR (< 0.01 mg/kg). Parent pyriproxyfen and/or its related metabolites were never detected in wheat grain and straw. It is noted that the metabolites 4'-OH-PYR and PYPAC have very low to moderate persistence (max. laboratory DT_{90} of 148 and 179 days, respectively) and might be taken up by the following crops. However, the available field soil dissipation studies showed that the highest concentration of 4'-OH-PYR (0.03 mg eq/kg) occurred in soil up to 3 days after the last treatment and residues of PYPAC were never detected in any of the soil dissipation studies (< 0.01 mg eq/kg) (see Section 4). Since single residue fraction did not exceed 0.01 mg eq/kg in the rotational crops planted at 30-day PBI, it is not expected that residues > 0.01 mg eq/kg for 4'-OH-PYR and PYPAC would be observed in rotational crops planted at longer PBIs. Further studies addressing the fate of 4'-OH-PYR and PYPAC residues in rotational crops are therefore not needed and a residue definition is not deemed necessary for the rotational crops.

Pyriproxyfen was shown to be stable under frozen conditions for up to 12 months in tomatoes (high water content matrices), 4 months in oranges (high acid content matrices) and 13 months in cotton seed (high oil content matrices). It is noted that according to the current guidelines storage stability data on a commodity representative of the pome fruit crop group are also required in order to support the representative use on apples and pears and covering the maximum storage time interval of the residue samples from the submitted trials on apples (data gap).

A sufficient number of GAP-compliant residue trials on oranges and mandarins (southern European Union (SEU) outdoor GAP) with an extrapolation to the whole group of citrus fruit, on tomatoes (indoor GAP) and on apples (SEU outdoor GAP) with an extrapolation to pears are acceptable. The validity of the residue trials on apples is however pending on the outcome of the assessment of the requested storage stability data on pome fruit. Since only seven GAP-compliant residue trials on tomatoes (SEU outdoor GAP) are available, one additional residue trial on tomatoes is requested to complete the SEU outdoor residue data set (data gap).

Pyriproxyfen can be considered as hydrolytically stable under conditions representative of pasteurisation, baking/brewing/boiling and sterilisation. Residue trials were submitted to derive processing factors for processed commodities of tomatoes, cotton and citrus fruits.

From the representative uses, the livestock dietary burden calculation triggered investigation of pyriproxyfen residues in ruminants only. Metabolism studies on laying hens and lactating goats with both labellings were provided and considered valid. In poultry, pyriproxyfen was predominant in eggs, muscle and fat (46–94% TRR). In liver and kidney, it was extensively degraded into numerous minor metabolites and a significant fraction of radioactive residues being associated with proteins. 2-OH-PY and 4'-OH-PYR (free and sulfate conjugates) were identified at relevant proportions (> 10% TRR) in eggs, liver, muscle and fat. For ruminants and for both labellings, pyriproxyfen was extensively degraded in milk, liver and kidney (< 1–15% TRR) with 4'-OH-PYR (free and sulfate conjugates) being predominant in those matrices (18–53% TRR), 2,5-OH-PY (conjugate) in milk (30% TRR), POPA in liver (16% TRR) and POP sulfate conjugate in kidney (36% TRR). Parent compound and 4'-OH-PYR (free and sulfate conjugated) were predominant in muscle (44% and 22% TRR, respectively) and in fat (79% TRR and 30% TRR, respectively). At the calculated dietary burden for ruminants, the transfer of total residues was insignificant in milk and tissues (< 0.01 mg/kg) and a default residue definition for **monitoring** and **risk assessment** is set as pyriproxyfen for animal matrices. MRLs are not required for products of animal origin. Since the representative uses are not feed items for fish, metabolism and feeding studies are not required.

The consumer dietary risk assessment has been performed using the EFSA Pesticide Residues Intake Model (PRIMo rev.2A) and the toxicological reference values agreed for pyriproxyfen. The highest chronic exposure to pyriproxyfen residues was calculated for Dutch children, representing 7.5% of the ADI of pyriproxyfen. The acute dietary intake accounted for a maximum of 6.2% of the ARfD of pyriproxyfen for

oranges (UK infant). However, the consumer risk assessment cannot be finalised in view of the identified data gaps. Although a case has been provided by the applicant that on a chemical point of view, isomerisation between *R*- and *S*-isomers of pyriproxyfen is unlikely to occur, a preferential metabolisation of the enantiomers in plants cannot be excluded. However and in view of the large margin of safety observed in the dietary intake calculation, it can reasonably be assumed that the potential complete degradation of the racemic mixture to a potentially more toxic enantiomer in plant matrices will have a negligible impact on the consumer toxicological burden. Finally, the consumer risk assessment is not finalised with regard to the unknown nature of residues that might be present in drinking water, consequent to water treatment processes following abstraction of surface water that might contain pyriproxyfen and its metabolites (see Section 4).

The investigation on residue levels in pollen and in bee products for human consumption with regard to the representative uses on citrus fruit, apples, pears and tomatoes is not required. For citrus fruit, treatment takes place after flowering. For pome fruit, significant residues are not expected in apples and pears at the flowering stage in view of the low translocation of pyriproxyfen residues observed from the metabolism data. Tomato crop has no melliferous capacity according to the current guidelines (European Commission, 2018).

3.2. Maximum residue levels

An MRL application has been submitted to modify the current EU MRL on citrus fruit. Sufficient and acceptable residue trials were submitted to derive an MRL for citrus fruit. As the intended use on citrus fruit was the same as the representative use, the use in this MRL application does not trigger a revision of the calculated livestock dietary burden and the consumer dietary risk assessment.

4. Environmental fate and behaviour

Pyriproxyfen was discussed at the Pesticides Peer Review TC 201 in January 2019.

Pyriproxyfen is a racemic mixture of an (*R*)-enantiomer and an (*S*)-enantiomer. The methods of analyses used in the radiolabelled soil and water studies in the dark were able to distinguish between the enantiomers and there was no significant change in the isomeric ratio over the duration of the studies. However, this information was not available for metabolites 4'-OH-Pyr, PYPAC and DPH-Pyr, which contain chiral carbon atom, and to address the specific environmental behaviour of the single isomers of pyriproxyfen under illuminated conditions. Therefore, for those processes in which microbial metabolism is involved, some degree of enantioselective transformation in the environment cannot be excluded. This is identified as a data gap (see Section 7). However, except for the chronic risk assessment to aquatic invertebrates for metabolite PYPAC, this data gap did not result in an assessment not finalised for parent pyriproxyfen (soil compartment) and metabolites DPH-Pyr (aquatic environment), 4'-OH-Pyr and PYPAC due to the margins of safety between hazard endpoints and PEC indicated in the available environmental risk assessments. For the aquatic risk assessment of pyriproxyfen, this uncertainty on the relative toxicity and contributions to the total residues levels of the isomers does not change the conclusion of high risk (see Section 5).

The rates of dissipation and degradation in the environmental matrices investigated were estimated using FOCUS (2006) kinetics guidance. In soil laboratory incubations under aerobic conditions in the dark, pyriproxyfen exhibited low to moderate persistence, forming the major (> 10% applied radioactivity (AR)) metabolite PYPAC (max. 13.9% AR), which exhibited very low to moderate persistence. In addition, metabolite 4'-OH-Pyr (max. 8.9% AR) exceeded 5% AR in at least two consecutive sampling dates in the degradation experiments; therefore, it was included in the present assessment. Metabolite 4'-OH-Pyr exhibited very low to moderate persistence. Mineralisation of the phenyl and pyridinyl ring ^{14}C radiolabels to carbon dioxide accounted for 11–42% AR and 21–61% AR after 90–120 days, respectively. The formation of unextractable residues for these radiolabels accounted for about 52% AR after 91–94 days (phenyl radiolabel) and 30–49% AR after 90–120 days (pyridyl radiolabel). No information on the degradation of pyriproxyfen under anaerobic conditions was submitted. Nevertheless, as anaerobic conditions are not likely to occur under representative uses, an anaerobic degradation study is not required. However, for uses of pyriproxyfen on other crops than the representative uses considered here, the importance of anaerobic conditions would need to be re-evaluated and metabolites formed under anaerobic conditions might need to be addressed further. Batch adsorption/desorption studies indicated that pyriproxyfen is expected to be immobile in soil. Metabolite 4'-OH-Pyr exhibited low to slight soil mobility, metabolite PYPAC exhibited very high soil

mobility and metabolite DPH-Pyr (a major metabolite in the aquatic compartment) exhibited medium to low soil mobility. It was concluded that the adsorption of pyriproxyfen and its metabolites was not pH dependent. In satisfactory field dissipation studies carried out at two sites in the US (spray application to the soil surface on bare soil plots in late spring), pyriproxyfen exhibited low persistence. Sample analyses were carried out also for metabolites PYPAC and 4'-OH-Pyr. Only very few soil composites collected for the two trials were found to contain detectable amounts of 4'-OH-Pyr (max. 0.03 mg/kg), while no residues of PYPAC were found in any samples collected. Reliable field DegT50 values were derived for pyriproxyfen following normalisation to FOCUS reference conditions (20° C and pF2 soil moisture) following the EFSA (2014a) DegT50 guidance. The field data endpoints were combined with laboratory values to derive modelling endpoints. In laboratory incubations in dark aerobic natural sediment water systems, pyriproxyfen exhibited low persistence, forming the major metabolites 4'-OH-Pyr (max. ca. 15% AR in sediment), PYPAC (max. ca. 24% AR in water) and DPH-Pyr (max. ca. 12% AR in water). The unextractable sediment fraction was the major sink for both the phenyl and pyridyl ^{14}C radiolabels, accounting for 31–51% AR at study end (100 days). Mineralisation of these radiolabels accounted for 11–52% AR at the end of the study. In aqueous photochemical degradation studies, pyriproxyfen degraded rapidly and it was concluded that no photodegradation products required further consideration in the exposure assessment. The necessary surface water and sediment exposure assessments (PEC calculations) were carried out for pyriproxyfen and metabolites 4'-OH-Pyr, PYPAC and DPH-Pyr using the FOCUS (2001) step 1 and step 2 approach (version 3.2 of the Steps 1-2 in FOCUS calculator). For the active substance pyriproxyfen and metabolites 4'-OH-Pyr and PYPAC, appropriate step 3 (FOCUS, 2001) and step 4 calculations (pyriproxyfen only) were available.[8] Only the step 4 calculations which appropriately followed the FOCUS (2007) guidance, with spray drift mitigation not exceeding 95% spray drift reduction, were accepted by the peer review. These mitigation measures applied at Step 4 modelling included no-spray drift buffer zones of up to 30 m for the field uses. The SWAN tool (version 4.0.1) was appropriately used to implement these mitigation measures in the simulations. For the representative uses on protected crops, the necessary surface water exposure assessment was appropriately carried out following the EFSA guidance on emission from protected crops (EFSA, 2014a). PEC_{sw} for pyriproxyfen and metabolites 4'-OH-Pyr and PYPAC were calculated for closed walk-in tunnels based on Step 3 drainage scenarios and for the use in high technology greenhouses, the specific model GEM (version 3.3.2) was used for both soil-bound and soil-less scenarios. For high-technology greenhouse uses the aquatic exposure does not cover the sediment compartment since the GEM assessment does not provide sediment PEC values, which could be particularly relevant for strongly adsorbed substances such as pyriproxyfen. This is identified as a data gap.

The necessary groundwater exposure assessments were appropriately carried out using FOCUS (European Commission, 2014a) scenarios and the models PEARL 4.4.4, PELMO 5.5.3 and MACRO 5.5.48.[8] The potential for groundwater exposure from the representative uses by pyriproxyfen and its 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 relevant FOCUS groundwater scenarios. For the representative uses in walk-in tunnels and high technology greenhouses, PEC_{gw} were calculated using the example Italian greenhouse scenario (Pistoia) in FOCUS PEARL (version 4.4.4) in line with the recommendations of the EFSA guidance document on protected crops (2014a). Also in this case, the potential for groundwater exposure above the parametric drinking water limit of 0.1 μg/L was concluded to be low for pyriproxyfen and its metabolites.

The applicant did not provide appropriate information to address the effect of water treatments processes on the nature of the residues that might be present in surface water and groundwater, when surface water or groundwater are abstracted for drinking water. This has led to the identification of a data gap (see Section 7) and results in the consumer risk assessment not being finalised (see Section 9).

The PEC in soil, surface water, sediment and groundwater covering the representative uses assessed can be found in Appendix A of this conclusion.

5. Ecotoxicology

The risk assessment was based on the following documents: European Commission (2002a,b), SETAC (2001), EFSA (2009), EFSA PPR Panel (2013) and EFSA (2013).

Pyriproxyfen was discussed at the Peer Review Experts' meeting 192 in February 2019.

[8] Simulations utilised the agreed Q10 of 2.58 (following EFSA, 2008) and Walker equation coefficient of 0.7.

The information to support the compliance of the batches used in ecotoxicological studies with the technical specification was considered sufficient.

Acute oral toxicity data on birds and mammals were available with the active substance pyriproxyfen. Short-term dietary and reproduction toxicity data on birds with pyriproxyfen were reported. Based on the available data and risk assessment, low acute and long-term risk from dietary exposure to **birds** was concluded for all the representative uses. Low acute and long-term risk from dietary exposure for **mammals** was concluded for all the representative uses with the exception of long-term risk for frugivorous mammals in citrus that required further refinement. Based on GAP-specific residue data on citrus, the risk was refined and a low long-term risk to frugivorous mammal was finally concluded for the uses in citrus.

Low risk to birds and mammals from exposure to contaminated water and via secondary poisoning was indicated for all the representative uses. For the metabolite 4'-OH-Pyr, relevant to soil and water compartments, no toxicity or BCF data were available. Considering, however, the chemical structure of the parent and of 4'-OH-Pyr, and the available aquatic- and soil-organism data, indicating that 4'-OH-Pyr is less toxic than the parent, a low risk from 4'-OH-Py via secondary poisoning to earthworm- and fish-eating birds and mammals was concluded for all the representative uses.

4'-OH-PYR was found in plant material (> 10% TRR). 4'-OH-PYR was detected in mouse and hen metabolism studies and the available data indicate that 4'-OH-PYR was covered in the mammalian and avian toxicity studies with the parent.[9] It was concluded that the risk to birds and mammals from 4'-OH-PYR is low.

Toxicity data for the active substance pyriproxyfen, and the pertinent aquatic metabolites 4'-OH-Pyr, DPH-Pyr and PYPA were available for all relevant aquatic organisms. Acute toxicity data with the representative formulation were available for fish, *Daphnia* and algae.

Based on the available tier 1 data, low acute risk for **fish** was concluded using FOCUS Step 1-3, for the representative uses in tomatoes (outdoor and soil-less greenhouse), ornamentals (outdoor, soil-less and soil-bound greenhouse) and for the walk-in tunnels (open and closed). A high acute risk was indicated using FOCUS Step 1-3, for the representative uses in citrus and for the majority of the FOCUS Step 3 scenarios (8 out of 10) in pome fruit (early) and in pome fruit (late) for 2 out of 10 FOCUS scenarios at Step 3 (R2/R3). A low acute risk for fish for the representative uses in citrus, pome fruit (early) and pome fruit (late; R2/R3) can be only concluded with appropriate mitigation e.g. buffer zones and/or spray drift reduction (FOCUS Step 4).

A low chronic risk to fish was concluded for the representative uses in tomatoes (soil-less greenhouse) and ornamentals (soil-bound greenhouse) and for walk-in tunnels (closed), using FOCUS Step 3. A low chronic risk for fish is indicated for the outdoor uses in tomatoes only with appropriate mitigation e.g. buffer zones and/or spray drift reduction (for all FOCUS scenarios at Step 4). For the outdoor uses in ornamentals, a low risk is indicated for the R2/R3 FOCUS scenarios at Step 4, provided that 10 m buffer/50% spray reduction is used. High chronic risk to fish cannot be excluded for the outdoor uses in citrus and pome fruit (late) using FOCUS Step 4, and in walk-in tunnels (open), and also for greenhouse soilless uses in ornamentals. For the uses in pome fruit (early), a high chronic risk to fish cannot be excluded for the D5/R2/R3 FOCUS scenarios at Step 4. A low risk for the rest of the uses in pome fruit (early) can be concluded only with appropriate mitigation measures.

The acute risk from pyriproxyfen to **aquatic invertebrates** was low for the outdoor and soil-less greenhouse uses in tomatoes and ornamentals, for the soil-bound greenhouse uses in ornamentals, and for the walk-in tunnels (closed), using FOCUS Step 1-3. For the outdoor uses in citrus, pome fruit (early and late application), tomatoes and ornamentals low acute risk was indicated using FOCUS Step 4 with mitigation measures. High acute risk for aquatic invertebrates was concluded for use in walk-in tunnels (open).

Based on standard laboratory studies, a high chronic risk to aquatic invertebrates was indicated for all the representative uses at FOCUS Step 3 & 4, with the exception of walk-in tunnels (closed) for which low risk was indicated at Step 3.

An indoor microcosm study was also available with the representative formulation. It was agreed that an assessment factor (AF) of 2 should be applied to the derived, from the microcosm study, no observed effect concentration (NOEC) of 1.2 μg a.s./L, due to identified uncertainties such as low number of sufficiently sensitive taxa, the absence from the microcosm study of *Daphnia magna*, the

[9] Refer to point 5(14) of the reporting table (EFSA, 2019).

most sensitive species in tier 1 tests. Therefore, an ETO-RAC of 0.6 μg a.s./L for aquatic invertebrates was established, while no ERO-RAC was considered possible.[10]

The PEC_{sw} values at FOCUS Step 3 were less than the ETO-RAC for the soil-less uses in tomatoes, the soil-bound uses in ornamentals and for the walk-in tunnels (closed) indicating low risk. The PEC_{sw} values at FOCUS Step 4 were less than the ETO-RAC for all the outdoor representative uses, whereas high risk was concluded for the soil-less greenhouse use in ornamentals and walk-in tunnels (open). Therefore a low chronic risk to aquatic invertebrates was indicated with mitigation, e.g. buffer zones and/or spray drift reduction, apart from the soilless greenhouse use (ornamentals) and for walk-in tunnels (open).

A risk assessment for the water phase based on PEC_{sw} FOCUS values was available for the **sediment-dwelling organisms**. The risk to sediment-dwelling organisms is low for the outdoor uses in tomatoes and ornamentals with mitigation measures such as a 5 m non-spray buffer zone for the use in tomatoes and 10 m non-spray buffer zone with 50% spray reduction for ornamentals. For the uses in pome fruits (early and late application) and citrus, PEC_{sw} FOCUS Step 4 values were available. A high risk could not be excluded for all the FOCUS scenarios at Step 4 in citrus, for 7 out of 10 scenarios in pome fruit (late) and the R3 FOCUS scenario in pome fruit (early). Therefore, the data from the available indoor microcosm study were further considered and a low risk to aquatic sediment-dwellers can be only concluded for the outdoor uses in citrus, and pome fruit (late and early application) with appropriate mitigation. On the basis of the microcosm study data, low risk was indicated (PEC_{sw} values at FOCUS Step 3 less than the ETO-RAC) for the soilless greenhouse uses in tomatoes, for the soil-bound greenhouse uses in ornamentals and for walk-in tunnels (closed). High risk is indicated for the soilless greenhouse use in ornamentals and for walk-in tunnels (open).

A risk assessment for the sediment compartment (using FOCUS PEC_{sed} values) was not available although it is triggered,[11] and therefore, a low risk cannot be concluded from exposure via the sediment (data gap and that could not be finalised).

Low risk to **algae** was concluded for all the representative uses at FOCUS Step 1-3. High risk was indicated for walk-in tunnels (open).

A low risk to **aquatic macrophytes** was indicated for all representative uses, using FOCUS Step 1-3. High risk was indicated for walk-in tunnels (open). However, the effect on *Lemna* was only 3.5% relative to the control treatment at the highest concentration tested (E_rC_{50} > 180 μg a.s./L) and the PEC/RAC was below 1.07. Overall, the risk was considered as low.

The PEC/RAC ratios were below 1 indicating low risk to aquatic organisms for the pertinent aquatic metabolites 4'-OH-Pyr, DPH-Pyr and PYPAC (FOCUS Step 1&2). However, given the uncertainty over the isomers for PYPAC (see Section 4) a conclusion for the risk from this metabolite could not be drawn (issue that could not be finalised).

As regards the risk assessment for bees (honeybees, bumble bees, solitary bees), a low risk was concluded for the situations when pyriproxyfen is used in high-technology greenhouses (tomato, ornamentals). The situation when pyriproxyfen is used in open-protected structures in tomato is covered by the available risk assessment for the outdoor use on tomato. As regards ornamentals, the RMS considered that the risk assessment for tomato would cover the risk for ornamentals. However, since the crop types which are included in the category of ornamentals is not defined, EFSA did not consider that the available risk assessments would cover the risk, when it is assessed with the EFSA guidance document (EFSA, 2013) from the outdoor use on ornamentals (data gap).[12]

Appropriate acute toxicity data on honey**bees** were available for the representative formulation. The risk assessment conducted according to the Guidance Document on Terrestrial Ecotoxicology (European Commission, 2002a) indicated a low acute contact and acute oral risk to honeybees (all representative uses). In addition to the acute data, appropriate chronic data were available for adult honeybees and larvae with the active substance. These data, together with the relevant acute data, were used in the tier 1 risk assessments for honeybees according to the EFSA Guidance Document (EFSA, 2013) for the representative uses on citrus, pome fruits and tomato (outdoor use). The calculations indicated a low contact and oral dietary risk to adult honeybees, but a high risk was indicated for the larvae. Appropriate endpoints to assess sub-lethal effects were not available and the available higher tier effect studies were not considered to be reliable (data gap).[13]

[10] Refer to experts' consultation 5.4 in the Report of Pesticides Peer Review experts' meetings 192 (EFSA, 2019).
[11] Refer to point 6 under Ecotoxicology, of the MS comments on the draft EFSA Conclusion on pyriproxyfen-ethyl Pesticides Peer Review Written Procedure: April-May 2019 (EFSA, 2019).
[12] Refer to Open point 5.26 in the evaluation table (EFSA, 2019).
[13] Refer to experts' consultation 5.5 in the Report of Pesticides Peer Review experts' meetings 192 (EFSA, 2019).

The risk via consumption of guttation fluid and contaminated surface water was assessed as low (all representative uses). No assessment was available for puddle water; however, the risk from this scenario was also considered as low on the basis of the risk assessment for guttation water.

Appropriate acute contact and oral toxicity data on bumblebees were available for pyriproxyfen and the risk assessment according to the EFSA guidance document (EFSA, 2013) indicated a low acute risk to bumble bees. Screening assessments were performed for chronic adult scenario and for the larval scenario for bumblebees. These calculations indicated that a high risk to bumble bees cannot be excluded for the representative uses on citrus, pome fruits and tomato (outdoor use). Screening assessments for solitary bees were also performed (acute adult, chronic adult, and larva). With the exception for the acute risk for the representative use on citrus, these calculations also indicated that a high risk to solitary bees cannot be excluded for the representative uses on citrus, pome fruits and tomato (outdoor use).

No data and quantitative risk assessments were available for the relevant plant metabolite 4'-OH-Pyr. However, the ecotoxicological profile of this metabolite was compared with that of the parent molecule that indicated that the metabolite has a comparable or lower toxicity than the parent (this assessment included data on arthropods and other invertebrates). Therefore, it was considered that the risk from metabolite the 4'-OH-Pyr is covered by the risk assessment for pyriproxyfen.

No assessment was performed for the accumulative toxicity.

Tier 1-toxicity and aged-residue tests on **non-target arthropods**, *Aphidius rhopalosiphi* and *Typhlodromus pyri*, were available with the representative formulation. A Tier 1-toxicity test on *Orius laevigatus* and an aged-residue test on *Chrysoperla carnea* with the representative formulation were additionally available. On the basis of the available data, high in-field risk was indicated for *T. pyri* for the representative uses in pome fruit, citrus, ornamentals and tomatoes. A low in-field risk to *A. rhopalosiphi* and *Orius laevigatus* was concluded for the representative use in pome fruit. For the representative uses in citrus, ornamentals and tomatoes, a low in-field risk was concluded only for *O. laevigatus*. A refined in-field risk assessment was available based on the aged-residue data on *T. pyri, A. rhopalosiphi* and *C. carnea*, with the representative formulation indicating, at the maximum application rate, less than 50% effects on reproduction after 14-day ageing. Therefore, a potential recolonisation within 1 year was indicated with the available data.

A low off-field risk to *A. rhopalosiphi* and *O. laevigatus* was concluded for all the representative uses, based on the available data. However, a high risk to *T. pyri* could not be excluded. A refinement of the risk, conducted with the endpoints from the aged-residue studies was available, considering only the effects from exposure to fresh residues, which were below 50% at relevant off-field dose rates. In conclusion, the off-field risk to non-target terrestrial arthropods was considered low.

On the basis of the available data and risk assessment, low risk to **earthworms** and other **soil macroorganisms**, **soil microorganisms, non-target terrestrial plants** and organisms in **sewage treatment plants** was concluded for all the representative uses.

With regard to the assessment of the **ED** potential of pyriproxyfen according to the ECHA and EFSA (2018), two fish short-term reproduction assays (level 3 study) and a fish full life cycle test with Medaka were available. In addition, a bird reproduction test and a fish early life stage test were also available. Based on the available data and assessment ED related adversity and endocrine activity was not identified. For the T modality, an amphibian metamorphosis assay was available. Effects on Hind Limb Length and delay in development were observed in the absence of histopathological changes. Therefore, in conclusion for non-target vertebrates, the ED criteria were not met for pyriproxyfen for the EATS modalities. It has to be noted, however, that pyriproxyfen is a juvenile hormone agonist in the target species. At this stage, no data and methods are available to further elucidate the specificity of the mode of action (MoA) for the target species and consequently possible endocrine mediated effects on non-target invertebrates. According to point 3.8.2 of Annex II to Regulation (EC) No 1107/2009, as amended by Commission Regulation (EU) 2018/605, it can be concluded that pyriproxyfen is not an endocrine disruptor for non-target arthropods.[14]

[14] Refer to experts' consultation 5.2 in the Report of Pesticides Peer Review experts' meetings 192 (EFSA, 2019).

6. Overview of the risk assessment of compounds listed in residue definitions triggering assessment of effects data for the environmental compartments (Tables 1–4)

Table 1: Soil

Compound (name and/or code)	Persistence	Ecotoxicology
Pyriproxyfen	Low to moderate persistence Bi-phasic DT_{50} 1.2–12.3 days (20–25°C and 75% 1/3 bar or 45% MWHC or pF2 soil moisture, DT_{90} 11–135 days) 2 US field dissipation studies single first-order (SFO) DT_{50} 9.2–9.5 days	Low risk to soil organisms
4'-OH-Pyr	Very low to moderate persistence SFO and biphasic DT_{50} 0.1–38 days (20–25°C and 75% 1/3 bar or 45% MWHC or pF2 soil moisture, DT_{90} 1–148 days)	Low risk to soil organisms
PYPAC	Very low to moderate persistence SFO and biphasic DT_{50} 1–54 days (20–25°C and 75% 1/3 bar or 45% MWHC or pF2 soil moisture, DT_{90} 7–179 days)	Low risk to soil organisms

DT_{50}: period required for 50% dissipation; DT_{90}: period required for 90% dissipation; MWHC: maximum water-holding capacity; pF2: pF value of 2 (suction pressure that defines field capacity soil moisture).

Table 2: Groundwater

Compound (name and/or code)	Mobility in soil	> 0.1 µg/L at 1 m depth for the representative uses[(a)]	Pesticidal activity	Toxicological relevance
Pyriproxyfen	Immobile K_{Foc} 11,820–35,728 mL/g	FOCUS GW: no	Yes	Yes
4'-OH-Pyr	Low to slight mobility K_{Foc} 953–3,564 mL/g	FOCUS GW: no	No	Unlikely to be genotoxic
PYPAC	Very high mobility K_{Foc} 9–31 mL/g	FOCUS GW: no	No	No Low acute oral toxicity *In vitro* genotoxicity: negative

K_{Foc}: Freundlich organic carbon adsorption coefficient; FOCUS: Forum for the Co-ordination of Pesticide Fate Models and their Use; GW: groundwater.
(a): FOCUS scenarios or a relevant lysimeter.

Table 3: Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Pyriproxyfen	High risk to aquatic organisms
4'-OH-Pyr	Low risk to aquatic organisms apart from the acute risk to fish
PYPAC	Low risk to aquatic organisms apart from the chronic risk to aquatic invertebrates
DPH-Pyr (water)	Low risk to aquatic organisms

Table 4: Air

Compound (name and/or code)	Toxicology
Pyriproxyfen	Rat and mouse LC_{50} > 1.3 mg/L air per 4 h (whole body, max attainable concentration)

LC_{50}: lethal concentration, median.

7. Data gaps

This is a list of data gaps identified during the peer review process, including those areas in which a study may have been made available during the peer review process but not considered for procedural reasons (without prejudice to the provisions of Article 56 of Regulation (EC) No 1107/2009 concerning information on potentially harmful effects).

7.1. Data gaps identified for the representative uses evaluated

- Surface tension studied at highest use-in concentration (relevant for all representative uses evaluated; see Section 1).
- Accelerated storage stability study (relevant for all representative uses evaluated; see Section 1).
- Verification of the extraction procedure used in the monitoring method in dry and high oil content matrices (relevant for all representative uses evaluated; see Section 1).
- Analytical method for monitoring of pyriproxyfen residues in body fluids (relevant for all representative uses evaluated; see Section 1).
- Further information and assessment of the analytical methods used in support of the (old) toxicity studies (relevant for all representative uses evaluated; see Section 1).
- For a complete literature review, the exclusion of articles after full-text assessment should be further justified (with the support of more detailed assessment of the full-text articles) (relevant for all representative uses evaluated; see Section 2).
- *In vitro* comparative metabolism with different animal species, including also human cell systems (relevant for all representative uses evaluated; see Section 2).
- Since pyriproxyfen is an UVB absorber, the *in vitro* phototoxicity test (OECD 3T3 NRU-PT) might not be appropriate, and phototoxicity/photogenotoxicity cannot be concluded. It is noted however that currently there is no OECD guideline available for UVB absorbers (relevant for all representative uses evaluated; see Section 2).
- Storage stability data for pyriproxyfen residues on a commodity representative of the pome fruit crop group (relevant for the representative use on apples and pears evaluated; see Section 3.1).
- One additional residue trial on tomatoes compliant with the SEU outdoor GAP (relevant for the representative use on tomatoes evaluated; see Section 3.1).
- Information on potential conversion/preferential degradation of isomers of pyriproxyfen in soil and water under illuminated conditions and in the water/sediment systems (concluded as not being necessary to conclude on the risk to terrestrial vertebrates and non target organisms for the representative uses evaluated; see Sections 4 and 5)
- Information on potential conversion/preferential degradation of isomers of metabolites DPH-Pyr (aquatic compartment only), 4'-OH-Pyr and PYPAC in the environmental compartments PYPAC (concluded as being necessary to conclude on the chronic risk assessment to aquatic invertebrates for metabolite PYPAC only for the representative uses evaluated; see Sections 4 and 5)
- PEC_{sed} calculations to address the risk assessment of sediment-dwelling organisms (relevant for the representative use in high-technology greenhouse uses (soil-less cultivations); see Section 4).
- Information to address the risk to sediment-dwelling organisms was not available and therefore a low risk could not be concluded for exposure via the sediment phase (relevant for all representative uses evaluated; see Section 5).
- Information to address the risk to honeybee larvae (relevant for all outdoor uses evaluated; See Section 5).
- Information to further address the risk to bees from the outdoor use on ornamentals (relevant for all outdoor uses evaluated; see Section 5).
- Information to address the risk from sublethal effects to bees (relevant for all outdoor uses evaluated; See Section 5).
- Information to address the effect of water treatment processes on the nature of residues present in surface water, when surface water is abstracted for drinking water was not available. Probably, in the first instance, a consideration of the processes of ozonation and chlorination would appear appropriate. If an argumentation is made that concentrations at the point of abstraction for drinking water purposes will be low, this argumentation should cover metabolites predicted to be in surface water, as well as the active substance. Should this consideration indicate novel compounds might be expected to be formed from water treatment, the risk to human or animal health through the consumption of drinking water containing them would need to be addressed (relevant for all representative uses evaluated; see Section 4).

7.2. Data gaps identified for the maximum residue level applications

No data gaps were identified for the MRL applications.

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

8.1. Particular conditions proposed for the representative uses evaluated

- Mitigation measures, e.g. no-spray buffer zone and/or spray drift reduction, should be applied for outdoor uses in citrus, pome fruit (early and late), tomatoes, ornamentals, and for greenhouse uses in ornamentals and tomatoes, to achieve a low risk for aquatic organisms (see Section 5).

8.2. Particular conditions proposed for the maximum residue level applications

No particular conditions are proposed for the MRL applications.

9. Concerns

9.1. Concerns for the representative uses evaluated

9.1.1. Issues that could not be finalised

An issue is listed as 'could not be finalised' if there is not enough information available to perform an assessment, even at the lowest tier level, for the representative uses in line with the uniform principles in accordance with Article 29(6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011[15] and if the issue is of such importance that it could, when finalised, become a concern (which would also be listed as a critical area of concern if it is of relevance to all representative uses).

An issue is also listed as 'could not be finalised' if the available information is considered insufficient to conclude on whether the active substance can be expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

1) In the absence of validated analytical methods to support most of the available (old) toxicological studies, their reliability could not be concluded upon (see Sections 1 and 2).
2) Comparative *in vitro* metabolism with possible identification of unique human metabolites could not be concluded (see Section 2)
3) The consumer dietary risk assessment could not be finalised in view of the identified data gaps for pyriproxyfen residues. In addition, the consumer risk assessment is not finalised considering the lack of appropriate information to address the effect of water treatment processes on the nature of residues potentially present in surface water, when surface water is abstracted for drinking (see Sections 3 and 4).
4) The chronic risk assessment to aquatic invertebrates for the pertinent aquatic metabolite PYPAC, could not be finalised (see Sections 4 and 5).
5) The risk assessment to sediment-dwelling organisms from exposure via the sediment could not be finalised (see Sections 4 and 5).
6) The risk assessment for bees from the field use on ornamentals (see Section 5).
7) The risk assessment for sublethal effects to honeybees could not be concluded (see Section 5).

[15] Commission Regulation (EU) No 546/2011 of 10 June 2011 implementing Regulation (EC) No 1107/2009 of the European Parliament and of the Council as regards uniform principles for evaluation and authorisation of plant protection products. OJ L 155, 11.6.2011, p. 127–175.

9.1.2. Critical areas of concern

An issue is listed as a critical area of concern if there is enough information available to perform an assessment for the representative uses in line with the uniform principles in accordance with Article 29 (6) of Regulation (EC) No 1107/2009 and as set out in Commission Regulation (EU) No 546/2011, and if this assessment does not permit the conclusion that, for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater, or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern if the assessment at a higher tier level could not be finalised due to lack of information, and if the assessment performed at the lower tier level does not permit the conclusion that, for at least one of the representative uses, it may be expected that a plant protection product containing the active substance will not have any harmful effect on human or animal health or on groundwater, or any unacceptable influence on the environment.

An issue is also listed as a critical area of concern if, in the light of current scientific and technical knowledge using guidance documents available at the time of application, the active substance is not expected to meet the approval criteria provided for in Article 4 of Regulation (EC) No 1107/2009.

- None

9.1.3. Overview of the concerns identified for each representative use considered

(If a particular condition proposed to be taken into account to manage an identified risk, as listed in Section 8, has been evaluated as being effective, then 'risk identified' is not indicated in Table 5.)

Table 5: Overview of concerns

Representative use		Citrus fruits	Pome fruit (apples, pears)	Tomatoes, field	Tomatoes, greenhouse	Ornamentals, field	Ornamentals, greenhouse
Operator risk	Risk identified						
	Assessment not finalised						
Worker risk	Risk identified						
	Assessment not finalised						
Resident/ bystander risk	Risk identified						
	Assessment not finalised						
Consumer risk	Risk identified						
	Assessment not finalised	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Risk to wild non-target terrestrial vertebrates	Risk identified						
	Assessment not finalised						
Risk to wild non-target terrestrial organisms other than vertebrates	Risk identified	X[(c)]	X[(c)]	X[(c)]		X[(c)]	
	Assessment not finalised	X[5,7]	X[5,7]	X[5,7]	X[5]	X[5,6,7]	X[5,6]
Risk to aquatic organisms	Risk identified	X	X	X		X	
	Assessment not finalised	X[4,5]	X[4,5]	X[4,5]	X[4,5]	X[4,5]	X[4,5]

Representative use		Citrus fruits	Pome fruit (apples, pears)	Tomatoes, field	Tomatoes, greenhouse	Ornamentals, field	Ornamentals, greenhouse
Groundwater exposure to active substance	Legal parametric value breached						
	Assessment not finalised						
Groundwater exposure to metabolites	Legal parametric value breached[(a)]						
	Parametric value of 10 μg/L[(b)] breached						
	Assessment not finalised						

The superscript numbers relate to the numbered points indicated in Sections 9.1.1 and 9.1.2. Where there is no superscript number, see Sections 2–6 for further information.

(a): When the consideration for classification made in the context of this evaluation under Regulation (EC) No 1107/2009 is confirmed under Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008.

(b): Value for non-relevant metabolites prescribed in SANCO/221/2000-rev. 10 final, European Commission, 2003.

(c): The high risk to honeybee larvae was identified on the basis of the tier 1 risk assessment of EFSA, 2013. Pyriproxifen is an IGR, therefore reliable higher tier studies would have been required considering both European Commission (2002a) and EFSA (2003).

9.2. Issues related to the maximum residue level applications

- None

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Abbreviations

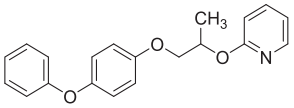
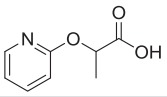
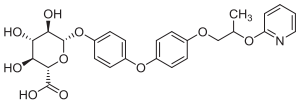
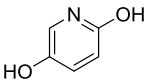
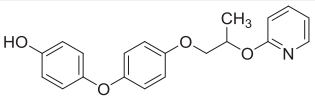
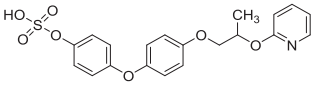
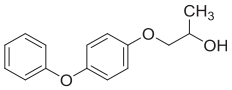
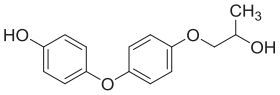
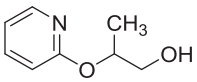
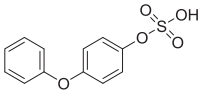
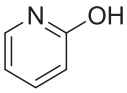
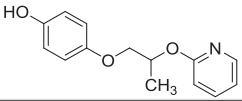
a.s.	active substance
AAOEL	acute acceptable operator exposure level
ADI	acceptable daily intake
AF	assessment factor
AOEL	acceptable operator exposure level
AR	applied radioactivity
ARfD	acute reference dose
BCF	bioconcentration factor
bw	body weight
CAS	Chemical Abstracts Service
CIPAC	Collaborative International Pesticides Analytical Council Limited
DAR	draft assessment report
DT_{50}	period required for 50% dissipation (define method of estimation)
DT_{90}	period required for 90% dissipation (define method of estimation)
EATS	Oestrogen, androgen, thyroid or steroidogenic
EC	emulsifiable concentrate
ECHA	European Chemicals Agency
EEC	European Economic Community
ErC_{50}	effective concentration (growth rate)
ERO	ecological recovery option
ETO	ecological threshold option
FAO	Food and Agriculture Organization of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	Good Agricultural Practice
GC	gas chromatography
HPLC-MS/MS	high-pressure liquid chromatography with tandem mass spectrometry
InChiKey	International Chemical Identifier Key
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JMPR	Joint Meeting of 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_{Foc}	Freundlich organic carbon adsorption coefficient
LC	liquid chromatography
LC_{50}	lethal concentration, median
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LDH	lactate dehydrogenase
LOAEL	lowest observable adverse effect level
LOQ	limit of quantification
M/L	mixing and loading
MoA	mode of action
MRL	maximum residue level
MS	mass spectrometry
MWHC	maximum water-holding capacity
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NPD	nitrogen–phosphorus detector
OECD	Organisation for Economic Co-operation and Development

PEC	predicted environmental concentration
PEC_{air}	predicted environmental concentration in air
PEC_{gw}	predicted environmental concentration in groundwater
PEC_{sed}	predicted environmental concentration in sediment
PEC_{soil}	predicted environmental concentration in soil
PEC_{sw}	predicted environmental concentration in surface water
pF2	pF value of 2 (suction pressure that defines field capacity soil moisture)
PPE	personal protective equipment
QSAR	quantitative structure–activity relationship
RAC	regulatory acceptable concentration
RAR	Renewal Assessment Report
RMS	rapporteur Member State
SEU	southern European Union
SFO	single first order
SMILES	simplified molecular-input line-entry system
TRR	total radioactive residue
UF	uncertainty factor
UV	ultraviolet
WHO	World Health Organization

Appendix A – List of end points for the active substance and the representative formulation

Appendix A can be found in the online version of this output ('Supporting information' section): https://doi.org/10.2903/j.efsa.2019.5732

Appendix B – Used compound codes

Code/trivial name[a]	IUPAC name/SMILES notation/InChiKey[b]	Structural formula[b]
Pyriproxyfen	4-phenoxyphenyl (*RS*)-2-(2-pyridyloxy)propyl ether CC(OC1=NC=CC=C1)COC2=CC=C(OC3=CC=CC=C3)C=C2 NHDHVHZZCFYRSB-UHFFFAOYSA-N	
PYPAC	2-[(pyridin-2-yl)oxy]propanoic acid CC(C(O)=O)OC1=NC=CC=C1 INLOHHUITHYIOO-UHFFFAOYSA-N	
4′-OH-pyriproxyfen glucuronide	4-(4-{2-[(pyridin-2-yl)oxy]propoxy}phenoxy)phenyl β-D-glucopyranosiduronic acid O[C@H]1[C@@H]([C@@H](C(O)=O)O[C@H]([C@@H]1O)OC2=CC=C(OC3=CC=C(OCC(OC4=NC=CC=C4)C)C=C3)C=C2)O KADFZEVCUBZCAR-LEMJXWAQSA-N	
2,5-OH-PY	pyridine-2,5-diol OC1=NC=C(O)C=C1 CHGPEDOMXOLANF-UHFFFAOYSA-N	
4′-OH-PYR	4-(4-(2-(pyridin-2-yloxy)propoxy)phenoxy)phenol CC(OC1=NC=CC=C1)COC2=CC=C(OC3=CC=C(O)C=C3)C=C2 LRAGDWMWQOLALS-UHFFFAOYSA-N	
4′-OH-PYR sulfate conjugates	4-(4-(2-(pyridin-2-yloxy)propoxy)phenoxy)phenyl hydrogen sulfate CC(OC1=NC=CC=C1)COC2=CC=C(OC3=CC=C(OS(O)(=O)=O)C=C3)C=C2 HDDYYMKTLXTYSP-UHFFFAOYSA-N	
POPA	1-(4-phenoxyphenoxy)propan-2-ol CC(O)COC1=CC=C(OC2=CC=CC=C2)C=C1 RVAHBQKJLFMRFE-UHFFFAOYSA-N	
4′-OH-POPA	4-(4-(2-hydroxypropoxy)phenoxy)phenol CC(O)COC1=CC=C(OC2=CC=C(O)C=C2)C=C1 RDORWJHXEWLXOT-UHFFFAOYSA-N	
PYPA	2-(pyridin-2-yloxy)propan-1-ol CC(OC1=NC=CC=C1)CO XYMSWYULCWBKHX-UHFFFAOYSA-N	
POP sulfate conjugates	4-phenoxyphenyl hydrogen sulfate O=S(OC1=CC=C(OC2=CC=CC=C2)C=C1)(O)=O BGBLXCAVHFWLJR-UHFFFAOYSA-N	
2-OH-PY	pyridin-2-ol OC1=NC=CC=C1 UBQKCCHYAOITMY-UHFFFAOYSA-N	
DPH-Pyr	4-(2-(pyridin-2-yloxy)propoxy)phenol OC(C=C1)=CC=C1OCC(C)OC2=NC=CC=C2 OEEXMCPZWLJVDE-UHFFFAOYSA-N	

IUPAC: International Union of Pure and Applied Chemistry; SMILES: simplified molecular-input line-entry system; InChiKey: International Chemical Identifier Key.
(a): The metabolite name in bold is the name used in the conclusion.
(b): ChemBioDraw v.13.0.2.3021.