PEER REVIEW REPORT ON **PYRIPROXYFEN** 21 07 2009

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1. Identity, Physical and chemical properties, Details of uses and further information, Methods of analysis

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	Section 1 Open points: ***7*** Points for clarification: ***3*** Data gaps: ***5***			Section 1 Open points: ***2*** Points for clarification: ***0*** Data gaps: ***6***
	Open point: 1.1 The agreed template for the list of endpoints should be used. See reporting table 1(1)		December 2008: The LoEP has been amended to the agreed template. February 2009: List of endpoints amended.	PRAPeR 61 (13 – 16 January 2009) Open point open. Written procedure Open point fulfilled The end points have been amended.
	Data gap: 1.1 Confirmatory method for the identity of impurity 2 has been identified as a data gap. The applicant has stated that this was submitted to the RMS in January 2006 See reporting table 1(2)	Notifier: A new study (NNA-0097) was submitted to the RMS in January 2006 to confirm the identity of Impurity #2 in pyriproxyfen technical material responding to the question raised on the draft DAR from RMS. The RMS has acknowledged the receipt of this study.	December 2008: See addendum to Vol. 4 (December 2008).	PRAPeR 61 (13 – 16 January 2009) Data gap turned into a point of clarification. Point of clarification addressed.

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1.1	Point of clarification for the applicant The commercial availability of the starting materials should be provided. Especially for [redacted] if this is not commercially available a specification and method of manufacture should be provided. See reporting table 1(3)	Notifier: Information on the commercial availability of the starting materials, especially for [redacted] was provided from different manufacturer (Japanese and Chinese) and was submitted to the EFSA by the agreed deadline of 01 December 2007	December 2008: MSDS of [redacted] is provided. Point clarified.	PRAPeR 61 (13 – 16 January 2009) Point of clarification addressed.
1.2	Point of clarification for the applicant: [redacted] and therefore if they are not relevant impurities they should be removed from the specification. See reporting table 1(5)	Notifier: Although agreeing that the technical specification should be based on the current 5-batch analysis, the notifier would prefer to keep [redacted] in the specification. The reasons for this request is that the level of these impurities in technical material depends on the composition of the starting materials. The level of [redacted] in starting materials are fluctuating, therefore, the notifier wishes to retain [redacted] for these two impurities in the specification. This information was submitted to the EFSA by the agreed deadline of 01 December 2007	December 2008: See addendum to Vol.4 (December 2008). The level on the specification for both impurities should be kept at [redacted]	PRAPeR 61 (13 – 16 January 2009) Point of clarification closed. New data gap proposed, see below.

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	New data gap: 1.6 Identified at PRAPeR 61 meeting. The applicant should provide QC data to support the specification unless the non-relevant impurities in question are removed from the specification.			PRAPeR 61 (13 – 16 January 2009) Data gap open. Written procedure Data gap remains
	Data gap: 1.2 The biological activity of the isomers has not been tested and this has been identified as a data gap. The applicant has stated that they will provide the data in December 2007. See reporting table 1(6)	Notifier: Information can be found in the publication from Kramer et al, Modern Crop Protection Compounds, 25 Insect molting and metamorphosis, WILEY-VCH Verlag GmbH & Co. KgaA (p797 – 811). Based on the results, the activity ratio of the (R)- and (S)-forms of pyriproxyfen was about 1 : 9 (R:S) This information was submitted to the EFSA by the agreed deadline of 01 December 2007.	December 2008: See addendum to Vol.4 (December 2008).	PRAPeR 61 (13 – 16 January 2009) Data gap open. Written procedure Data gap remains But it will be noted that a paper was presented but that it could not be taken in to account because of Reg 1095/2007

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	Data gap: 1.3 GLP studies for relative density, spectra (IR, 1H-NMR and Mass), water solubility at pHs 5, 7 and 9, and partition coefficient at pHs 5, 7 and 9 have been identified as a data gap. The applicant has stated that these were submitted in January 2006. See reporting table 1(12)	Notifier: New GLP studies for relative density, spectra (IR, 1H-NMR and Mass), water solubility at pHs 5, 7 and 9, and partition coefficient at pHs 5, 7 and 9 were submitted to the RMS in January 2006. The RMS has acknowledged the receipt of these studies.	December 2008: GLP studies for IR, ^{1}H NMR and MS spectra, water solubility and partition coefficient have been submitted. B2 (revised Vol3, December 2008) and LoEP have been amended accordingly.	PRAPeR 61 (13 – 16 January 2009) Data gap open. Written procedure Data gap remains But it will be noted that the data are available but that they could not be taken in to account because of Reg 1095/2007.
	Open point: 1.2 Rapporteur should clarify what the correct vapour pressure is. See reporting table 1(16)	Notifier: The RMS could mistakenly have revised the vapour pressure of <1.33 x 10-5 Pa as shown in Open point 1(16) of the reporting table and described it in the endpoint lists. The report states a vapour pressure of < 1.0 x 10-7 mmHg at 22.81ºC, hence the correct value should be <1.33 x 10-5 Pa as indicated in the DAR. Based on point 1(17) of the reporting table, the notifier submitted a new report for Henry's law constant in which the correct vapour pressure (<1.33 x 10-5 Pa) is used for the calculation.	December 2008: The report states the vapour pressure being <1.0x10^{-7} Pa. B2 (revised Vol3, December 2008) and LoEP are amended accordingly.	PRAPeR 61 (13 – 16 January 2009) Open point closed.

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	Data gap: 1.4 A new calculation of Henry's Law constant should be made using the new water solubility study has been identified as a data gap The applicant has stated that this will be available in December 2006. See reporting table 1(17)	Notifier: The RMS has acknowledged the receipt of the new study for water solubility and a new calculation of Henry's Law constant has been provided. This recalculation of the Henry's Law constant for pyriproxyfen was presented by the notifier in a new study report (NNP-0113). Calculated value < 7.37 × 10−2 Pa m3 mol−1 This information was submitted to the EFSA by the agreed deadline of 01 December 2007.	December 2008: Henry Law's constant has been recalculated with the correct vapour pressure being $<1.0x10^{-7}$ Pa and results from the new water solubility study. The calculated value $<7.37x10^{-4}$ has been amended in the LoEP and B2 (revised Vol3, December 2008).	PRAPeR 61 (13 – 16 January 2009) Data gap open. Written procedure Data gap remains But it will be noted that the data are available but that they could not be taken in to account because of Reg 1095/2007.
	Open point: 1.3 The following four new studies submitted to the RMS in January 2006 - Report No. NNP-0102 (Relative Density) - Report No. NNP-0104 (Spectroscopic Properties (IR, NMR, MS)) - Report No. NNP-0105 (Water Solubility) - Report No. NNP-0103 (n-Octanol/Water Partition Coefficient) can not be considered in accordance with Regulation 1095/2007 See reporting table 1(29)		December 2008: RMS disagrees that these studies can not be taken into account as they were submitted before December 1st 2007. Revised Vol 3 (December 2008) and LoEP have been amended.	PRAPeR 61 (13 – 16 January 2009) Open point closed.

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	Open point 1.4 Under B.2.2 In the methods and results column it appears that a lot of the text in the original template used to make this document has been left in by mistake. This makes the table unclear and it should be amended. See reporting table 1(30)		December 2008: The table under B2.2. is amended in the revised volume 3 (December 2008).	PRAPeR 61 (13 – 16 January 2009) Open point closed.
1.3	Point of clarification for the applicant: The oxidising properties of the formulation needs to be addressed. See reporting table 1(31)	Notifier: The available study following US EPA study guidelines is fully valid to support the EU requirement for oxidising properties of a liquid product like Pyriproxyfen 10 EC	December 2008: No new studies or reasoned statement is submitted as was requested. Therefore still point of clarification for the applicant.	PRAPeR 61 (13 – 16 January 2009) Point of clarification turned into data gap, see below.
	New data gap: 1.7 Identified at PRAPeR 61 meeting. The applicant to provide information on the oxidising properties of the formulation.			PRAPeR 61 (13 – 16 January 2009) Data gap open. Written procedure Data gap remains

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	Open point: 1.5 The packaging material B.3, further information on the ppp states PE/EVOH but in column 3 the rapporteur states PE/PB. What is PE/PB. See reporting table 1(33)	Notifier: This issue will be addressed at Member State National re-registrations	December 2008: In the reporting table it is stated that notifier should provide information on the container material, RMS agreed on that. This should not be considered as an open point. PB generally stands for polybutadiene. However no new studies or reasoned statement as requested is submitted. To be addressed at Member State level.	PRAPeR 61 (13 – 16 January 2009) Open Point closed. New data gap proposed, see below.
	New data gap: 1.8 Identified at PRAPeR 61 meeting. The applicant to provide information on the packaging material. Depending on what information is provided further storage stability data may be required to address the interaction of the formulation with the commercial packaging.			PRAPeR 61 (13 – 16 January 2009) Data gap open. Written procedure Data gap remains
	Open point: 1.6 The need for R65 classification should be discussed by a meeting of experts. See reporting table 1(36)	Notifier: Agree with the UK and the RMS that R65 is not required based on the trigger for surface tension not being reached.	December 2008: To be discussed by a meeting of experts.	PRAPeR 61 (13 – 16 January 2009) Open point closed.

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	Data gap: 1.5 The need for a method of analysis for plants including ILV and a confirmatory method if necessary. has been identified. See reporting table 1(40)	Notifier: Request clarification as to which plant matrices and what additional validation is necessary? In the reporting table the RMS considers the plant method for high water containing matrices to be adequate. Reasoned arguments are presented in the ILV report (Study 2) as to why a verification ion <m/z 100 was selected. The lower mass number of 78 originates from the phenyl group being detached via ether cleavage from pyriproxyfen and should be one of the confirmation mass numbers. Notifier agrees with the RMS that no further validation is necessary for water containing commodities. For commodities with high fat content the original method validation (Study 3) was successfully performed on cotton seed. ILV of this method (Study 4) shows successful validation on olives. Therefore in terms of primary methodology a suitable validation of a method for commodities with high fat content has been adequately demonstrated. Therefore sufficient information is also considered to have been submitted for analysis of crops with high fat content. According to Official Journal of the European Union, L 19/23, 24.1.2006, a	December 2008: The method provided for high water content is considered adequately validated. ILV of the method for high fat content shows indeed successful validation on olives. Confirmatory methods however should be submitted. Notifier should provide adequate methods, irrespective the availability of methods elsewhere used in the world.	PRAPeR 61 (13 – 16 January 2009) Data gap closed.

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		monitoring programme for pyriproxyfen in several crops is underway. Crops are apples (acid commodity), head cabbage, leek, lettuce, tomatoes, peaches including nectarines and similar hybrids (watery commodities), rye or oats (dry commodities), and strawberries (watery). Therefore, a suitable monitoring method must be available in EU. Also, a new MRM using LC/MS/MS has been developed in Germany and pyriproxyfen is listed as being recoverable. Since official MRMs are available for pyriproxyfen in several crops in EU, it seems that any further validation is not required. Confirmation is therefore requested as to whether further validation is necessary.		
	Open point: 1.7 The validation data for the confirmatory soil and water methods should be provided in an addendum. It is noted that the data were available when the DAR was written. See reporting table 1(42)		December 2008: According to SANCO 825/00 and SANCO 3029/99 no (full) validation for confirmatory methods is required. These methods are to demonstrate specificity, this has been demonstrated at LOQ and 10x LOQ. At LOQ recoveries have been calculated for 3 fortifications. They were virtually the same as those reported for the GC-NPD method. Vol.3 has been amended.	PRAPeR 61 (13 – 16 January 2009) Open point closed.

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	New open point: 1.8 Identified at PRAPeR 61 meeting. RMS to amend the list of end points according to the discussions during the PRAPeR 61 meeting.		February 2009: List of endpoints amended.	PRAPeR 61 (13 – 16 January 2009) Open point open. Written procedure Open point fulfilled The end point have been amended.

2. Mammalian toxicology

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	Section 2 Open points: ***21*** Points for clarification: ***1*** Data gaps: ***0***			Section 2 Open points: ***1*** Points for clarification: ***0*** Data gaps: ***0***
	Open point 2.1 RMS to provide more details on the study of Isobe (1988a) to clarify the calculation of oral absorption. See reporting table 2(1)	Notifier: The oral absorption rate of 63% proposed in the dossier is already a worst case estimate. The absorption value is very important because it affects the AOEL and the value of 40% is not consistent with the data and is unnecessarily conservative. As unchanged pyriproxyfen was not eliminated in bile the pyriproxyfen in faeces is the unabsorbed dose and this can be used to calculate absorption. This is a more scientific approach as it avoids mixing data from different experiments. The basis for the calculation of the amount of the low and high dose absorbed should be made more clear in the DAR. In particular, the problem which arises from the lack of a determination of radioactivity in the residual carcass at the end of the bile fistula experiment should be stated. On page 57 the absorption of 39-49% is said to be based on radioactivity recovered from urine, bile and tissues whereas on page 70 and page 144 the	December 2008: See addendum (December 2008). The summary of the study of Isobe as presented in the DAR is copied, and the calculation of oral absorption is explained and amended. The RMS still proposes to use 40% for oral absorption. To be discussed in the expert meeting.	PRAPeR 64 (19 -23 01.2009): Open point fulfilled. The agreed oral absorption value is 40%.

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		same range is quoted based on urine, CO2, tissues, cage wash, residual carcass and bile. The values used to calculate absorption and the experiments from which they are taken need to be explained in more detail. For highly lipophilic compounds, lower oral absorption can be observed with bile-duct cannulated rats compared with normal rats because of a shortage of bile acid or slow gastrointestinal motility caused by physical restraint of rats. As unchanged pyriproxyfen was not eliminated in bile the pyriproxfen in faeces has not been absorbed whereas the metabolites in faeces of normal rats have been absorbed. This can be used as the basis of a more scientific approach for estimating absorption as it avoids mixing data from different experiments. Absorption rate (%) = dose (100%) - unabsorbed compound in normal rats (% of the dose) = dose (100%) - pyriproxyfen detected in faeces with normal rats (% of the dose) The amount of pyriproxyfen in faeces of rats was 21%-37.2% after single (2 or 1000 mg/kg) administration of [phenoxyphenyl-14C]pyriproxyfen or [pyridyl-2,6-14C]pyriproxyfen, and it		

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		was decreased to 6.5%-11.4% after repeated (2 mg/kg) administration. Therefore, the absorption rate was 63%-79% after single administration and 89-93% after repeated administration to normal rats. Notifier considers that the oral absorption rate of 63% proposed in the dossier is already a worst case estimate. The proposed value of 40% is not consistent with the data and is unnecessarily conservative.		
	Open point 2.2 (RMS's proposal) Oral absorption value to be discussed by the experts. See reporting table 2(1)	Notifier: See comments on Open point 2.1.	December 2008: See open point 2.1.	PRAPeR 64 (19 -23 01.2009): Open point closed (see 2.1).
2.1	Point of clarification for the applicant: historical control data for changes in clinical chemistry have to be provided. The applicant announced the submission of these data for the 1st December 2007. See reporting table 2(3)	Notifier: Historical control data were submitted to the EFSA by the agreed deadline of 01 December 2007	December 2008: The historical control data is presented in the addendum (December 2008).	PRAPeR 64 (19 -23 01.2009): Point of clarification addressed.
	Open point 2.3	Notifier: This point is of lesser	December 2008:	PRAPeR 64 (19 -23 01.2009):

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	NOAEL in the subacute inhalation study to be discussed by the experts. RMS could provide a revised table 6.3.3.1 with additional figures for the discussion. See reporting table 2(3)	importance as it does not affect the reference doses. However the increased LDH and slight changes of some organs weights in male at 1000 mg/m3 should be considered of little toxicological significance. These differences were marginal, showed no dose-dependency, were within physiological changes, and there were no related histopathological changes or no statistically significant changes In addition, according to the historical control data, all LDH values except one animal at 1000mg/m3 are within the normal level calculated on the assumption that mean +/- 2SD. The animal excepted above showed no change in relevant parameters, so that the Notifier considers it as incidental. Therefore, the increased LDH should be considered of little toxicological significance.	The study is presented in more detail in the addendum (December 2008). As the notifier already pointed out, the NOAEL of this study does not affect the overall risk assessment. The RMS still proposes a NOAEL of 482 mg/m^3 (as was proposed in the study report), although it is recognised that the effects are indeed marginal.	Open point fulfilled. Agreed NOAEC in the 28-day rat inhalation study = 482 mg/m^3/day (4h/day, whole body).
	Open point 2.4 NOAEL in the 52-week dog study to be confirmed by the experts. RMS could provide a revised version of the table 6.3.4.4 with additional figures in order to ease the discussion.	Notifier: The changes of cholesterol levels and liver weights were slight or marginal and only occurred in one of the four males at 30 mg/kg bw/d. Although the Notifier recognises that this does not affect the NOAEL it does affect the consideration of the AOEL.	December 2008: Additional figures are presented in the addendum (December 2008). The RMS still proposes a NOAEL < 30 mg/kg bw/day for males and a NOAEL of 30 mg/kg bw/day for females. It should be taken into account that the second 52-week dog study with a NOAEL of 10 mg/kg bw/day is the critical study for	PRAPeR 64 (19 -23 01.2009): Open point fulfilled. Agreed NOAEL in the first 52-week dog study (Chapman, 1991) < 30 mg/kg bw/day (males).

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	See reporting table 2(4)		the risk assessment.	
	Open point 2.5 NOAEL in the 2-year rat study to be confirmed by the experts. RMS could provide a revised table 6.5.1.1 with additional figures in order to ease the discussion by the experts. See reporting table 2(6)	Notifier: The increased incidence of dark area in the liver was noted in only females at 3000 mg/kg food and no histopathological changes related to this change were observed. Therefore, this finding was not treatment-related. In addition the histopathological changes noted in liver were generally secondary to some other cause of death and not treatment-related since no incidence of liver necrosis was noted in the rats sacrificed at week 53 and week 105. However the areas of disagreement do not affect the NOAEL for the study.	December 2008: All relevant figures are already presented in the DAR. Please note that the notifier agrees with the derived NOAEL! Dark areas in the liver: This finding was observed, possibly treatment-related and thus described in the table. This finding, however, does not trigger the derivation of the NOAEL. RMS still considers that this finding should be presented in the DAR. Histopathological changes in the liver (necrosis): An increased incidence of liver necrosis was only noted in animals that died before the end of the treatment period. The incidence of liver necrosis among the unscheduled deaths was 35% (8/23) and 25% (4/16) for the males and females, respectively, in the 3000 mg/kg bw/d group. The RMS considers this a relevant finding and does not agree with the notifier that this finding should be deleted from the DAR.	PRAPeR 64 (19 -23 01.2009): Open point fulfilled. The agreed NOAEL in the 2-year rat study is 27.2 mg/kg bw/day based on liver findings (clinical chemistry and increased weight).
	Open point 2.6 Adversity of the liver findings in the rat 2-generation study to be discussed by the experts (with regard to the setting of the NOAEL).	Notifier: The NOAEL for parental toxicity was 1000 mg/kg food and not 200 mg/kg food as proposed by the RMS. The increase in relative liver weights in F1 males at 1000 mg/kg food was not adverse because there were	December 2008: All relevant figures are already presented in the DAR. The parental NOAEL should be discussed, which is based on increased relative liver weight. This figure is presented in the	PRAPeR 64 (19 -23 01.2009): Open point fulfilled. In the 2-generation rat study, the agreed

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	RMS could provide a revised table 6.6.1.1 with additional figures in order to ease the discussion. See reporting table 2(12)	no histopathological changes of liver even in the highest dose group, in which the histopathological examination of liver in all F1 males was conducted. The effects were marginal, there was no absolute organ weight change and no histopathological change that was consistent with the weight change. Therefore, the NOAEL for parental toxicity was 1000 mg/kg food. This conclusion is consistent with the result of a JMPR evaluation	DAR: relative liver weight at 1000 mg/kg food is 110% of control. Liver is target organ of pyriproxyfen and the increased liver weight at 1000 mg/kg food is the start of a dose-response. The increase is indeed marginal, but histopathology was not performed on all animals of the 200 and 1000 mg/kg food groups and no clinical biochemistry was performed. The parental NOAEL is not critical for the overall risk assessment. To be discussed in the expert meeting.	parental NOAEL is 200 ppm (13.3 mg/kg bw/day), the offspring NOAEL is 1000 ppm (66.7 mg/kg bw/day) and the reproductive NOAEL is 5000 ppm (333.3 mg/kg bw/day).
	Open point 2.7 RMS to provide a revised table 6.6.1.2 with additional figures and historical control data in order to confirm the NOAELs in the combined rat teratogenicity and reproductive study. See reporting table 2(16)	Notifer: Agrees that the NOAEL is 1000 mg/kg/day and has no additional comments.	December 2008: Additional figures and historical control data are presented in the addendum (December 2008). Conclusion: NOAELmales <100 mg/kg bw/day NOAELmat 100 mg/kg bw/day NOAELdev 1000 mg/kg bw/day No teratogenic effects.	PRAPeR 64 (19 -23 01.2009): Open point fulfilled. In the combined rat teratogenicity and reproductive study, the agreed NOAELs were: - for the offspring: 1000 mg/kg bw/d - for the parents: <100 mg/kg bw/d - for repro/terato: 1000 mg/kg bw/d
	Open point 2.8 NOAELs in the rat teratogenicity study to be confirmed by the experts. RMS could provide a revised table 6.6.2.1 with additional figures instead of statements in order to ease the	Notifier: The increase in early implantation loss was not statistically significant and consequently it was considered not treatment related. This does not affect the NOAEL for the study.	December 2008: A revised table 6.6.2.1 is presented in the addendum (December 2008). The conclusion does not change. NOAELmat 100 mg/kg bw/day NOAELdev 100 mg/kg bw/day No teratogenic effects.	PRAPeR 64 (19 -23 01.2009): Open point fulfilled. In the rat teratogenicity study, - the agreed maternal NOAEL is 100 mg/kg bw/day.

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	discussion. See reporting table 2(18)			- the agreed developmental NOAEL is 100 mg/kg bw/day.
	Open point 2.9 NOAELs in the peri-post natal rat study to be confirmed by the experts. RMS could provide a revised table 6.6.2.3 with additional figures in order to ease the discussion. See reporting table 2(23)	Notifier: Although the NOAEL is not affected the findings (increased incidences of renal pelvis dilatation and hyperaemia and/or inflammatory cell infiltration in the propria of the urinary bladder) observed in a peri- and postnatal toxicity study should be removed from lists of critical effects in the above sections. At necropsy of the offspring after 3 weeks postpartum, increased incidences of dilatation of the renal pelvis, and hyperemia and/or inflammatory cell infiltration in the propria of the urinary bladder were noted in the 500 and 300 mg/kg bw/day dose groups, but no such effects were seen in offspring examined at 8 weeks postpartum. Moreover, no renal pelvis dilatation was observed in foetuses in the rat teratogenicity study. Therefore, the findings were thought to be growth retardation, but not visceral anomalies	December 2008: As the notifier already pointed out, there is no discussion about the NOAELs of the study. The Member States did not comment on the NOAELs and there is just discussion on interpretation of some findings that are not the critical findings for setting the NOAEL. For this peri-post natal study no OECD guideline is available. It is true that not all values are reported in detail, but this study is acceptable because it produces some additional information, and based on Table 6.6.2.3 the picture is clear. The dossier further contains acceptable OECD guideline teratogenicity studies with rat and rabbit, and this peri-post natal study confirms the findings and NOAELs in these studies.	PRAPeR 64 (19 -23 01.2009): Open point fulfilled. In the peri-post natal rat study, the agreed maternal and developmental NOAEL is 100 mg/kg bw/d.
	Open point 2.10 Experts to confirm the NOAELs in the rabbit teratogenicity study (maternal and developmental).	Notifier: The NOAEL for teratogenicity in the rabbit study should be >300 mg/kg in both the table and in paragraph 4 as no developmental effects were found even at 1000 mg/kg.	December 2008: In the DAR, the RMS proposed: NOAELmat 100 mg/kg bw/day NOAELdev 300 mg/kg bw/day No teratogenic effects.	PRAPeR 64 (19 -23 01.2009): Open point fulfilled. In the rabbit teratogenicity study,

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	See reporting table 2(24)		The number of dams remaining in the top dose group of 1000 mg/kg bw/d was insufficient to draw reliable conclusions. To be discussed in the expert meeting.	- the agreed maternal NOAEL is 100 mg/kg bw/day - the agreed developmental NOAEL is 300 mg/kg bw/day
	Open point 2.11 Setting of the ARfD to be discussed by the experts See reporting table 2(27)	Notifier: It is unnecessary to set an ARfD for pyriproxyfen. The only acute toxicity alert is for mortality in the mouse acute toxicity study which occurs at 2000 mg/kg bw. The ARfD proposed is 10 mg/kg bw which has no practical value because such a dose could not be achieved from the consumption of residues. The calculations for the NESTI and IESTI intake using the proposed ARfD confirm that NESTI and IESTI are negligible, and do not exceed 0.07% by Dutch and UK models and 0% by FAO/WHO models for both adults and children (See details in Volume 3, Annex B, B.7.15.). The EU Guidance for setting an acute reference dose (7199/VI/99 rev 5) states that one of the criteria for not setting an ARfD is that the pesticide is of very low acute oral toxicity (e.g. no adverse clinical signs and deaths have been observed at the limit dose for LD50 testing) (Chapter 4.4). However, this does not mean that an ARfD must be set if there are adverse clinical signs	December 2008: The RMS acknowledges that the 'Guidance for setting an ARfD' was very strictly interpreted. The RMS decided to present the 'worst-case option' (setting an ARfD) in the DAR as starting point for the discussion. However, considering the toxicological profile of pyriproxyfen and the very high value which was derived for the ARfD (10 mg/kg bw/day) it can indeed be questioned if an ARfD is required. To be discussed at the PRAPeR meeting whether it is necessary to set an ARfD.	PRAPeR 64 (19 -23 01.2009): Open point fulfilled.

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		or deaths at the limit dose in an individual study. Although the RMS considers that deaths in the mouse study at a dose of 2000 mg/kg mean that it is necessary to set an ARfD, the Notifier does not consider this is a correct interpretation of the guidance. With regard to the comment from DE concerning use of the developmental toxicity study mortalities occurred after on days 4, 5, 6, 7 and 9 which was only after at least 4 daily dose had been received. Consequently the mortality in this study is not relevant to an endpoint which is based on an acute effect. The EU guidance (Section 1.4)a) and Solecki et alb) also mentioned that developmental effects, which occur only at doses that produce maternal toxicity, may not be considered relevant for ARfD setting. In this study, excessive maternal toxicities, such as maternal death, were observed in the 1000 mg/kg/day dose group. In the group at 300 mg/kg/day or more, the incidence of fetuses with an opening of the foramen transversarium of the 7th cervical vertebra was significantly higher than that of control group but only occurred at dose that were considered maternally toxic. However, this finding is such a skeletal variation as follows; 1) this finding has been		

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		observed in the historical control data, 2) the increase incidence of this finding was only observed in the groups with maternal toxicities, and 3) there were no statistically significance in the incidence of pups between the control and treatment groups at postnatal day 21. There is no critical developmental issue and no evidence of teratogenicity in the developmental toxicity study in rats with pyriproxyfen; therefore, it is inadequate for setting ARfD based on the results of this study. The relationship between the ARfD and the consumption of residues also needs to be considered when deciding whether an ARfD is required. There is no result in residues in food that will exceed the value proposed by the RMS. The calculations for the NESTI and IESTI intake using the proposed ARfD confirm that NESTI and IESTI are negligible, and do not exceed 0.7% by Dutch and UK models. The EU guidance (7199/VI/99 rev 5) states that under the above circumstances an ARfD is not necessary. a) Guidance for the setting of an acute reference dose, European Commission, Health and Safety Directorate, 7199/VI/99 rev.5, 5 July 2001 b) Solecki, R. et al., Guidance of setting of acute reference dose (ARfD) for		

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		pesticides, Food Chem. Toxicol., 43, 1569-1593 (2005)		
	Open point 2.12 Derivation of the AOEL to be discussed by the experts (relevant species, relevant study, correction for oral absorption) See reporting table 2(28)	Notifier: The AOEL should be based on the NOAEL from the short-term toxicity study, 23.5 mg/kg bw/day in the 13-weeks oral toxicity study in rats. It is not appropriate to select the NOEL of 10 mg/kg bw/day, from the 1-year study in dogs for pyriproxyfen. For tomato and eggplant, the RMS considers that it cannot be excluded that the exposure duration of re-entry activities will exceed 3 months. However, based on Notifier's experience of the actual use for tomato and eggplant in a glasshouse, a maximum of two applications per growing season are claimed (two crop cycles per year making four applications per year) which leads to a max 80 days of exposure (20 hectare treated 4 times per year, 2 treatments per crop cycle with 2 cycles per year, makes 80 hectares treated in one year). Worst case is a hand held sprayer or knapsack sprayer on the back with a maximum of 1 hectare treated per day. This makes a maximum 80 days exposure to the product during application in this extreme worst case. Even if chronic exposure occurs by the re-entry activities, it is not appropriate	December 2008: See the addendum (December 2008) for an overview of all relevant studies. Because there seems to be no effect of exposure duration (for the rat, for the dog this is not completely clear since there is no chronic dog study), the RMS selected the dog as most sensitive species and used the 1-year dog study for derivation of the AOEL. Since the most relevant NOAEL in the dog studies is derived from the 1-year dog study, the RMS considers the AOEL applicable for semi-chronic and chronic exposure. The notifier proposes to derive the AOEL based on the 13-week rat study with a NOAEL of 23.5 mg/kg bw/day. However, in case a semi-chronic AOEL should be derived, the 2-generation study with rats is also a semi-chronic study with a more critical NOAEL of 13.3. To be discussed in the expert meeting.	PRAPeR 64 (19 -23 01.2009): Open point fulfilled. The agreed AOEL is 0.04 mg/kg bw/day (SF 100, oral absorption 40%). The agreed ADI is 0.1 mg/kg bw/day (SF 100).

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		to select the NOEL of 10 mg/kg bw/day, from the 1-year study in dogs. The RMS considered that the NOAELs from the 13-weeks and 6-months studies (23.5 and 24.0 mg/kg bw/day, respectively) in rats were too close to the LOAEL of 30 mg/kg bw/day from the 1-year oral toxicity study in dogs. However, the effects at the LOAEL of 30 mg/kg bw/day were very slight. The NOAEL for females was 30 mg/kg bw. As for male dogs, there were minimal effects on cholesterol levels and liver weights (caused by only one male dog out of 4 dogs), but no histopathological changes in the liver were observed at the LOAEL of 30 mg/kg bw/day. Therefore, it can be assumed that the real NOAEL in this study is just slightly lower than 30 mg/kg bw/day.		
	Open point 2.13 RMS to revise the list of end points also taking into consideration the discussion at the meeting of experts. See reporting table 2(30)		December 2008: The list of endpoints has been revised based on the comments in the reporting table and based on the addendum (December 2008). If necessary, the list of endpoints will again be revised after the expert meeting.	PRAPeR 64 (19 -23 01.2009): Open point fulfilled.
	Open point 2.14 Dermal absorption values to be confirmed by the experts. See reporting table 2(31)	Notifier: Agrees with the values proposed in the DAR, 2.5% for the concentrate and 13% for the spray strength.	December 2008: To be discussed in the expert meeting. RMS still proposes 2.5% for the concentrate and 13% for the spray dilution, based on *in vitro* dermal	PRAPeR 64 (19 -23 01.2009): Open point fulfilled.

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			absorption data with human skin.	The agreed dermal absorption values were 2.5% for the concentrate and 13% for the dilution
	Open point 2.15 RMS to provide revised exposure calculations (with final results in % of AOEL) after agreement of the AOEL. See reporting table 2(32)		December 2008: To facilitate the discussion, the RMS already presented the exposure calculations in the addendum (December 2008), with final results in % of AOEL, using the AOEL proposed in the DAR (0.04 mg/kg bw/day). In case the AOEL changes during the expert meeting, the risk assessment can easily be amended.	PRAPeR 64 (19 -23 01.2009): Open point fulfilled.
	Open point 2.16 Bystander exposure to be confirmed by the experts (with regard to the parameters used in the calculations). See reporting table 2(33)		December 2008: See open point 2.15 and the addendum (December 2008). The calculations for the bystander are now presented in a new transparant spreadsheet, and in the addendum (December 2008) a body weight of 60 kg is assumed for the bystander.	PRAPeR 64 (19 -23 01.2009): Open point fulfilled.
	Open point 2.17 Detailed calculations of operator exposure with the Dutch greenhouse model to be provided in an addendum (December 2008). See reporting table 2(34)		December 2008: See open point 2.15 and the addendum (December 2008). The calculations for the operator with the Dutch greenhouse model are now presented in a new transparant spreadsheet.	PRAPeR 64 (19 -23 01.2009): Open point fulfilled. New open point proposed, see below.
	New open point 2.22:		February 2009: See the revised addendum (Jan. 2009).	PRAPeR 64 (19 -23 01.2009):

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	RMS to provide new operator exposure estimates with the Dutch model for the indoor use (without the use of RPE) in a revised addendum.		In the original addendum (December 2008) discussed at PRAPeR 64, the use of RPE was by mistake taken into account for the indoor use in Southern Europe. That resulted in 11% of the AOEL with PPE and RPE. In the revised addendum (Jan. 2009), operator exposure for indoor use in Southern Europe with PPE (gloves and coverall) is 15% of the AOEL. The correct value (15% of AOEL) was already presented in the List of Endpoints which was amended during the PRAPeR 64 meeting.	Open point open. Written procedure Open point fulfilled.
	Open point 2.18 Worker exposure to be discussed by the experts with regard to the used model and parameters, and additional calculations with Europoem II to be provided in an addendum (December 2008). See reporting table 2(37)		December 2008: See open point 2.15 and the addendum (December 2008). The calculations for the worker are now presented in a new transparant spreadsheet. EUROPOEM II was used for the calculations.	PRAPeR 64 (19 -23 01.2009): Open point fulfilled.
	Open point 2.19 Experts to discuss whether the level of toluene (relevant impurity) in the final technical specification is covered by its level in the toxicological batches.	Notifier: The test material used in the toxicology studies is representative of the technical specification supported for Annex I inclusion	December 2008: To be discussed in the expert meeting.	PRAPeR 64 (19 -23 01.2009): Open point fulfilled. Toluene is a toxicologicall relevant impurity but not of concern at the proposed level in the T.S (0.5%).

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	See reporting table 2(40)			
	Open point 2.20 Experts to discuss the relative toxicity of the plant metabolite PYPA ((RS)-2-(2-pyridyloxy)propyl alcohol) in comparison with pyriproxyfen, taking into account that it is proposed as intermediate in the rat metabolic pathway but has not been identified in the rat metabolism studies. The notifier has provided a position in his comments on the reporting table. See reporting table 2(41)	Notifier: The response provided previously still applies. Although the metabolite was not found in rat, it would be formed from metabolism of the ether bond and is an intermediate in the biotransformation of pyriproxyfen. The toxicology of PYPA is taken into account in the toxicological profile of pyriproxyfen	December 2008: See the addendum (December 2008) for more information. To be discussed in the expert meeting.	PRAPeR 64 (19 -23 01.2009): Open point fulfilled. PYPA is most probably an intermediate in the rat metabolism, and is therefore covered by the reference values of the parent.
	Open point 2.21 As pyriproxyfen is produced as a racemic mixture of enantiomers (R/S), can the adverse effects observed during the toxicological studies be attributed specifically to one of the isomers ? This is to be discussed by the experts. See reporting table 2(42)	Notifier. The mixture of enantiomers in the test material used in the toxicology studies is the same as that in the technical material supported for Annex I inclusion	December 2008: To be discussed in the expert meeting.	PRAPeR 64 (19 -23 01.2009): Open point fulfilled. No information is available on the relative toxicity of the individual isomers.

3. Residues

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	Section 3 Open points: ***6*** Points for clarification: ***0*** Data gaps: ***0***			Section 3 Open points: ***1*** Points for clarification: ***0*** Data gaps: ***0***
	Open point 3.1 The RMS assessment: 'The metabolite was not found in rat, but should be the only logic product of hydrolysis of the ether bond of pyriproxyfen. It's toxicology is taken into account in the toxicological profile of pyriproxyfen.' should be confirmed by the meeting of toxicology, in order to agree that the proposed relevant residue in food and feed items is pyriproxifen only. see also comment 3(14) A revision of the respective paragraph with regard to the length of the PHI should be done in a revised DAR/ corrigendum as appropriate. See reporting table 3(2)	Notifer: Agree with the RMS position on this point and note that the DOR is accepted as pyriproxyfen only in reporting table 3(14).	December 2008: To await conclusion of PRAPeR 64 (toxicology).	PRAPeR 65 (19 -23 01.2009): Open point fulfilled. The meeting on toxicology has agreed that PYPA is likely to be an intermediate in the rat metabolism and that it is covered by the toxicological reference values of pyriproxyfen. It is not necessary to include PYPA in the plant residue definition as a relevant metabolite.
	Open point 3.2		December 2008:	PRAPeR 65 (19 -23 01.2009):

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	Considerations on potential livestock exposure through cotton gin trash and resulting residues in food of animal origin to be transferred in an addendum to the DAR See reporting table 3(18)		Potential livestock exposure was calculated using the OECD feeding table for Europe and the Lundehn feeding table. It was found that the trigger value for performing livestock feeding studies was not exceeded. Comparison of exposure of livestock with the feeding level used in the metabolism studies showed that no residues have to be expected. See addendum to the DAR (December 2008).	Open point fulfilled. Addendum of Dec 2008 was discussed by the meeting.
	Open point 3.3 RMS proposal: To be discussed in an expert meeting whether gin trash should be dealt with as a feed item See reporting table 3(18)		December 2008: Cotton will be grown in Bulgaria, Spain and Greece. Livestock can potentially be exposed to cotton seed(products) or gin trash. It was calculated using the OECD and Lundehn feeding tables that residues have not to be expected. See addendum to the DAR (December 2008).	PRAPeR 65 (19 -23 01.2009): Open point fulfilled. Cotton gin trash can be considered as a minor feed item within EU.
	Open point 3.4 With view on the higher persistency of metabolite 4-OH-PYR to be discussed by experts whether the succeeding crops issue (in particular the potential for accumulation in crops at higher DAT) is sufficiently addressed by the available	Notifier: The confined rotational crop study of pyriproxyfen is conducted at the application rate of 80 g a.i./acre (197.7 g a.i./ha). The concentration of radioactivity in the treated soil is calculated to be 12 ppm (equiv. to pyriproxyfen) considering the application rate and method used for this study. The aerobic soil metabolism study shows that 4'-OH-Pyr is formed at	December 2008: Measuring 4-OH-PYR in rotational crops planted 30DAT showed that no residues of 4-OH-PYR exceed 0.01 mg/kg. Since it was calculated that at higher DAT the level of 4-OH-PYR is lower than the level measured in the rotational crop study performed at	PRAPeR 65 (19 -23 01.2009): Open point fulfilled. The meeting of experts considered that no further data in succeeding crops should be required.

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	data. See reporting table 3(19)	0.9-6.3 % AR (Applied Radioactivity) in soil 1 to 30 days after treatment. Therefore, succeeding crops in the confined rotational crop study are exposed not only to pyriproxyfen but also to 4'-OH-Pyr at a level of at least 0.108 ppm, assuming that 0.9 %AR of pyriproxyfen is transformed during the 30-day plant back period. The concentration of 0.108 ppm corresponds to ten times greater than the value calculated as the maximum plateau concentration, 0.013 ppm (SE), reached one year after application at the tomato GAP. As a result, no conspicuous residue including 4'-OH-Pyr was detected from the quantitative and qualitative aspects in the confined succeeding crops. In the U.S. field dissipation study, no persistency of 4'-OH-Pyr. 4'-OH-Pyr was found (<0.01 mg/kg) at any time 10 days after the last application and no carryover was found immediately after multiple applications with a 14-day interval, except for one of three sites. At this site, 4'-OH-Pyr was detected at a maximum of 0.02 mg/kg during Day 0 to 7 after the last application and the residue at Day 30 was only 0.003 mg/kg. These results indicates that DT50 of 4'-OH-Pyr should be less than 10 days in the actual field and this is	30DAT, no residues of 4-OH-PYR should occur in rotational crops at higher DAT. See addendum to the DAR (December 2008). Overall, it can be concluded that 4-OH-PYR levels in soil are lower in the field than calculated based on lab DT50 values. No residues of 4-OH-PYR have to be expected in rotational crops since.	

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		clearly faster than the calculated DT50 of 24 to 70 days (mean 38 days) from the laboratory studies which were conducted under the worst case situation. Although the storage stability study showed that 20-40% of the residue of 4'-OH-Pyr in soil might be degraded during the storage in the field dissipation study, the rate of dissipation of 4'-OH-Pyr in the field could not be affected by the stability. Even taking the degradation into consideration, the maximum formation of 4'-OH-Pyr in the field would be estimated at double of 0.02 mg/kg, namely 0.04 mg/kg. Considering the above comprehensively, the possibility of uptake of 4'-OH-Pyr to succeeding crops is unlikely and at insignificant levels, even if it occurs.		
	Open point 3.5 To be agreed by MSs that the number of available residue trials in cotton is sufficient for risk assessment purposes (and to establish a reliable MRL proposal) See reporting table 3(23)	Notifier: Agree with the RMS that 2 residues trials should be sufficient to demonstrate a no residue situation based on the data generated to date.	December 2008: Two residue trials in which pyriproxifen was applied before boll opening, together with the results of the metabolism study performed at 2N, show that no residues have to be expected in cotton seed. See addendum to the DAR (December 2008).	PRAPeR 65 (19 -23 01.2009): Open point fulfilled. The meeting agreed that no further residue trials in cotton seed are necessary.
	Open point 3.6	Notifier: See data gap response for	December 2008:	PRAPeR 65 (19 -23 01.2009):

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	In view of the consumer risk assessment, MS to consider if data are sufficient to conclude whether the ratio of enantiomers may change due to preferential metabolism and/or degradation in the relevant matrices for the residues section See reporting table 3(24)	reporting table 1(6)	See addendum to the DAR (December 2008). No relevant information on metabolism plant was provided. Open point 2(21) on the toxicoloy of both metabolites was waived since all toxicological studies were performed with the racemic mixture as well. However, whether the (R) and (S) isomer show different metabolic patterns *in vivo* was not shown. A bridging study were both isomers are applied separately to plant is proposed. *New data gap*	Open point fulfilled. Data gap for formal reasons: Data are not sufficient to conclude on the ratio of enantiomers in crops. However, it was agreed that for the notified uses there should be no concern for the consumer since the margin of safety was considered sufficiently big given exposure is less than 2 % of the ADI, and no ARfD was set. If in future dietary exposure increases due to other uses, this issue has to be reconsidered.
	New open point 3.7: RMS to amend the list of end points according to the discussions during the PRAPeR 65 meeting.		February 2009: List of endpoints amended	PRAPeR 65 (19 -23 01.2009): Open point open. Written procedure: Open point fulfilled.

4. Environmental fate and behaviour

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	Section 4 Open points: ***7*** Points for clarification: ***2*** Data gaps: ***0***			Section 4 Open points: ***1*** Points for clarification:**0** Data gaps: ***0***
	Open point 4.1 RMS to annotate the LoEP rate of degradation in soil, laboratory studies, DT50 for 4-OH-Pyr to indicate that these values 'are dissipation rates (represent the sum of formation and degradation rate constants) estimated from the time point of the maximum observed concentration, in studies where pyriproxyfen was dosed.' See reporting table 4(6)		December 2008: We don't agree on the open point set. According to FK chapter 8.4.2. page 156 a conservative estimate for trigger values for the metabolite can be obtained by estimating the disappearance of the metabolite from its observed maximum. This is exactly the way that was chosen here. This approach can be used for calculating PECs and also for PECgw as it is a worst case estimate for the degradation of the metabolite. We don't agree on the wording that the value is a dissipation rate as it is still degradation that has been assessed. As the true maximum might have been higher compared to the observed maximum, the degradation rate in the decline phase may underestimate the true degradation rate. Therefore, the only wording suitable to add would be 'conservative estimate'.	PRAPeR 62 (13 – 15 January 2009) Open point open. RMS to annotate the LoEP rate of degradation in soil, laboratory studies, DT50 for 4-OH-Pyr to indicate that 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.' Written procedure Open point fulfilled The end points have been appropriately updated by EFSA.
4.1	Point of clarification for the applicant. Applicant to provide pKa	Notifier: It is not possible to draw any clear conclusions concerning the influence of pH on the adsorption of	December 2008: RMS agrees with notifier. Submitted information is included in the addendum	PRAPeR 62 (13 – 15 January 2009) Point of clarification addressed.

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	estimates (QSAR calculations) for the metabolites PYPAC and 4-OH-Pyr together with their argumentation how adsorption of pyriproxyfen PYPAC and 4-OH-Pyr would or would not be significantly affected at the pH range normally associated with agricultural soils. The applicant indicated that the requested clarification will be available by 01 December 2007. See reporting table 4(7)	metabolites 4'-OH-Pyr and PYPAC. No clear influence of pH was observed during the adsorption / desorption studies. Given their chemical properties, it is possible that adsorption of these metabolites may be pH dependent. However, based on the estimated pKa values for the metabolites, which are shown below, it can be assumed that the ionised form of these metabolites will not be significantly affected at the pH range normally associated with agricultural soils (pH 5.0 – 7.5). The dissociation constants (pKa) are estimated to be 2.06 and 4.35 for PYPAC, and 3.63 and 10.1 for 4'-OH-Pyr using the ACD/pK DB Program [Ver. 4.5, Advanced Chemistry Development (2000)]. This information was submitted to the EFSA by the agreed deadline of 01 December 2007, in Appendix 4.7.	(December 2008).	
	Open point 4.2 RMS to present clear accumulated soil PEC for metabolite 4-OH Pyr and the use on tomato / egg plant with the assumptions regarding the number of crops assumed to be planted per year clarified in an addendum. LoEP to be		December 2008: As the longest DT90 is<365 days it is not required to calculated PECacc. The provided calculations are superfluous. For tomatoes and eggplants in glasshouses in NE only one crop per year is grown. For SE tomato and eggplant only 1 crop per year is grown.	PRAPeR 62 (13 – 15 January 2009) Open point open. RMS to delete the accumulated soil PEC for tomato for '4'-OH-Pyr from the LoEP (soil accumulation and plateau concentration box) and replace with 'not required'.

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	updated as appropriate with these clarified accumulated 4-OH Pyr soil PEC. See reporting table 4(9)		Even if 2 crops per year are grown in Northern European glasshouses the carry over of soil residue is marginal. After 100 days the PECsoil TWA concentration is 0.005 mg/kg. For the metabolites 4'-OH-Pyr and PYPAC it is <0.001 mg/kg. The interval between 2 crops will always be larger than 100 days.	Written procedure Open point fulfilled The end points have been appropriately updated by the RMS.
	Open point 4.3 In the LoEP, RMS to delete '4'-OH-Pyr: maximum plateau concentration of 0.002 (SE) mg/kg reached after 1 year application on cotton of 1 x 75 g/ha (SE).' from the soil accumulation and plateau concentration box. See reporting table 4(9)		December 2008: As the longest DT90 is<365 days it is not required to calculated PECacc. Values referring to a PECacc should be deleted from the LoEP. But as there is no calculation in the first place there is nothing to delete.	PRAPeR 62 (13 – 15 January 2009) Open point open. In the LoEP, RMS to delete '4'-OH-Pyr: maximum plateau concentration of 0.002 (SE) mg/kg reached after 1 year application on cotton of 1 x 75 g/ha (SE).' from the soil accumulation and plateau concentration box. Written procedure Open point fulfilled The end points have been appropriately updated by the RMS.
4.2	Point of clarification for the applicant. Applicant to provide an assessment of the potential for groundwater exposure from pyriproxyfen or its metabolites 4-OH-Pyr and PYPAC as a result of the	Notifier: A FOCUS groundwater modelling assessment for the glasshouse tomato and eggplant uses was actually conducted for pyriproxyfen and its metabolites 4'-OH-Pyr and PYPAC and this modelling was submitted to the RMS with the original dossier for pyriproxyfen in November	December 2008: The FOCUS groundwater modelling for tomato field crop as surrogate for glasshouse use is included in the addendum (December 2008). It is questionable how relevant the predicted concentrations are for the application of pyriproxyfen in glasshouses. Climate	PRAPeR 62 (13 – 15 January 2009) Point of clarification addressed. New open point proposed, see below.

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	applied for uses in glasshouses. The applicant indicated that the requested clarification will be available by 01 December 2007. See reporting table 4(19)	2003 (SCC Report Nos.: NNW-0162, NNW-0163 and NNW-0164). As there are currently no FOCUS groundwater scenarios available that are relevant to protected crops, the simulations were based on the FOCUS scenarios for outdoor field tomatoes, which were selected as a worst-case surrogate. However, a revised FOCUS groundwater modelling assessment was subsequently conducted by the RMS using refined input parameters as reported in the DAR, and this assessment did not address the glasshouse uses. An evaluation of the available modelling which has been conducted in support of the field use on cotton and tomatoes demonstrates that predicted annual average concentrations of pyriproxyfen and its metabolites 4'-OH-Pyr and PYPAC were <0.001 µg/L in groundwater at 1m depth for all scenarios. These results clearly demonstrate that pyriproxyfen can be used safely within the EU without risk of concentrations of pyriproxyfen or its metabolites exceeding the 0.1 µg/L regulatory threshold in groundwater. As proposed in the reporting table 4(19), a worst-case groundwater modelling assessment for pyriproxyfen	conditions are usually optimised for plant growth and an excess of irrigation water is prohibited, the leaching conditions are not comparable to standard field conditions. Furthermore, there are no Northern European scenarios for tomatoes field use. However, RMS can agree that indoor uses are sufficiently covered by the simulation and that predicted concentrations in groundwater for indoor uses will not exceed 0.1 µg/L.	

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		and its metabolites 4'-OH-Pyr and PYPAC has been conducted to cover the glasshouse uses in Southern Europe. The simulations were based on application to field tomatoes at the maximum recommended application rate for glasshouse tomato and eggplant (2 x 0.1125 kg a.s./ha in Southern Europe), using the modelling input parameters listed in the DAR. Predicted concentrations of pyriproxyfen and 4'-OH-Pyr were <0.0000005 µg/L in all scenarios and predicted concentrations of PYPAC were highest in the Piacenza scenario (0.027 µg/L), but were always <0.1 µg/L. It is therefore considered that simulations on field tomatoes according to the GAP for indoor tomatoes and eggplants are sufficient to demonstrate that pyriproxyfen and its metabolites 4'-OH-Pyr and PYPAC will not reach 0.1 µg/L in groundwater following indoor uses on tomatoes and eggplants. This assessment was submitted to the EFSA by the agreed deadline of 01 December 2007, in Appendix 4.19.		
	New open point: 4.8 Identified at PRAPeR 62 meeting. RMS to include GW			PRAPeR 62 (13 – 15 January 2009) Open point open. Written procedure

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	assessment for greenhouse use in the LoEP.			Open point fulfilled The end points have been appropriately updated partly by the RMS and partly by EFSA..
	Open point 4.4 RMS to update the LoEP (photochemical oxidative degradation in air and PEC air method of calculation boxes) with the correct Atkinson method calculated atmospheric DT50 which should be consistent with the Physchem section of the endpoints. See reporting table 4(31)		December 2008: LoEP has been updated (December 2008).	PRAPeR 62 (13 – 15 January 2009) Open point fulfilled.
	Open point 4.5 RMS to add the reference Study Report No. NNP-0067, '4'-OH-Pyriproxyfen - Water solubility' to the separate list of information tests and studies relied on. (Report No. NNP-0068), the study title should be changed to 'PYPAC - Water solubility', in the separate list of information tests and studies relied on.		December 2008: Study Report No. NNP-0067, '4'-OH-Pyriproxyfen - Water solubility' has been included in the addendum (December 2008). The study was part of the original dossier and the endpoint has been used in the DAR. However, the study was not mentioned anywhere in the DAR. Probably because it was unclear if this should be part of section 1 or of section 7. The study title of Report No. NNP-0068 has been changed in the list of studies relied on.	PRAPeR 62 (13 – 15 January 2009) Open point open. RMS to add the reference Study Report No. NNP-0067, '4'-OH-Pyriproxyfen - Water solubility' to the document 'List of protected studies version 2-December 2008 Fate' and rename this document as 'list of information tests and studies relied on fate'. Written procedure Open point open RMS to rename the document 'List of

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	See reporting table 4(34)			protected studies version 3-February 2009 Fate' as 'list of information tests and studies relied on fate'.
	Open point 4.6 RMS to delete the reference Fathulla 1995a (anaerobic aquatic metabolism) from the separate list of information tests and studies relied on. See reporting table 4(35)		December 2008: Study deleted from the list of studies relied on.	PRAPeR 62 (13 – 15 January 2009) Open point fulfilled.
	Open point 4.7 RMS to update the separate list of information tests and studies relied on section for fate and behaviour by deleting the annex III references that were calculations that were not relied on. See reporting table 4(36)		December 2008: For PECgw calculations all information from notifiers reports was used except for the input values on DT_{50} and Koc, which were not agreed. Latest guidance was applied to derive the correct input values. For PECsw/sed in principle the same applies. Some input values were not agreed and therefore recalculation was done. Meeting to decide if these studies should be deleted or referred to.	PRAPeR 62 (13 – 15 January 2009) Open point open. RMS to reconsider which studies have been relied on (in the sense that at least some of the reports results have been transferred to the LoEP) and update the list of information tests and studies relied on accordingly Written procedure Open point fulfilled The list of information tests and studies relied on was appropriately updated by the RMS
	Message from PRAPeR 61 (Phys chem properties) The vapour pressure and the		December 2008: As this will not change the outcome of the risk assessment no new calculations have been performed.	PRAPeR 62 (13 – 15 January 2009) The message provided was noted by the meeting of fate and behaviour experts.

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	water solubility of pyriproxyfen has changed. Both values become lower.			
	New open point: 4.9 Identified at PRAPeR 62 meeting.			PRAPeR 62 (13 – 15 January 2009) Open point open. RMS to remove the suggestion for the residue definition for monitoring from the fate section of the LoEP. Written procedure Open point fulfilled The end points have been appropriately updated by the RMS.

5. Ecotoxicology

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	Section 5 Open points: ***11*** Points for clarification: ***0*** Data gaps: ***4***			Section 5 Open points: ***5*** Points for clarification: ***1*** Data gaps: ***4***
	Open point 5.1 RMS to include a risk assessment for birds and mammals from uptake of contaminated drinking water in an addendum. See reporting table 5(3)	Notifier: A risk assessment for birds and mammals has been provided in the DAR for exposure as a result of consumption of contaminated surface water. In addition, the Notifier has provided a worst-case assessment for exposure resulting from the uptake of diluted spray solution in leaf axils or from puddles, according to the guidance provided in SANCO/4145/2000. In conclusion, all TERa values are considerably greater than the Annex VI 91/414 EEC trigger of 10. Thus, in the case of birds the most severe value is >244 (small insectivorous bird on cotton) and for mammals it is a >1042 (small mammal on cotton). Hence, the acute risk to birds and mammals from the consumption of contaminated drinking water on a worst-case basis (uptake from leaf axils) is considered to be acceptable. This assessment was submitted to the EFSA by the agreed deadline of 01	December 2008: The risk assessment for birds and mammals from uptake of contaminated drinking water is included in the addendum (December 2008). The LoEP is also revised (December 2008), the new TERs are included.	PRAPeR 63 (13 – 15 January 2009) Open point fulfilled.

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		December 2007		
	Open point 5.2 RMS to include the TER values for fish, algae and Lemna in the LoEP. See reporting table 5(5)		December 2008: This was done. TERs for fish, algae and Lemna are presented in the LoEP (December 2008).	PRAPeR 63 (13 – 15 January 2009) Open point fulfilled. New open point proposed, see below.
	New open point: 5.12 Identified at PRAPeR 63 meeting. The meeting considered useful to have also the TER values for sediment dwellers and to include the endpoints for the formulation. RMS to update the LoE.		February 2009: TER values for sediment dwellers and endpoints for the formulation (aquatic toxicity studies) included in LoE. Proposal: open point closed.	PRAPeR 63 (13 – 15 January 2009) Open point open. Written procedure Open point fulfilled TER values for sediment dwellers and endpoints for the formulation (aquatic toxicity studies) were included in LoE.
	Open point 5.3 RMS to amend in the LoEP the level of residues after 14d depuration phase. See reporting table 5(6)	Notifier: The level of residues after 14d depuration phase in the bioconcentration table should be ≤10.4% (or rounded to 10%) rather than ≤11%	December 2008: LoEP has been revised (December 2008).	PRAPeR 63 (13 – 15 January 2009) Open point fulfilled.
	Open point 5.4 RMS to clarify in the LoEP the PECsw values used in the TER calculations for aquatic organisms		December 2008: Done. For each TER value for aquatic organisms, a note clarifies how the PECsw value was calculated.	PRAPeR 63 (13 – 15 January 2009) Open point fulfilled.

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	See reporting table 5(8)			
	Open point 5.5 MSs to discuss in an expert meeting the endpoint from the microcosm study and its use in the risk assessment and the safety factor which should be applied to the endpoint See reporting table 5(17)	Notifier: By considering the results of the microcosm study, such as NOECpopulation, NOECcommunity and recovery potential of the affected community and populations, the study design and natural ecology, it is proposed that the NOEAEC could be set at 20 µg a.s./L	December 2008: We consider the NOEAEC of 5.0 ug a.s./L to be the relevant endpoint from the microcosm study. Since this NOEAEC is set at a concentration at which the only effect was a slight transient direct negative effect on Daphnia galeata, which was observed only on one sampling point, we consider a safety factor not necessary. February 2009: Further details on the acceptability of the microcosm study as discussed during the meeting have been included in the revised Vol.3 of the DAR. Also, it was added that the assessment factor will be determined when information on the toxicity to insects is available (see new data gap 5.5). Proposal: Open point closed.	PRAPeR 63 (13 – 15 January 2009) Open point open. RMS to provide further details discussed during the meeting on the revised DAR. New data gap proposed, see below. Written procedure Open point fulfilled. Further information on the mesocosm study were provided during the meeting of experts, and subsequently included in a revised revision of the DAR.
	New data gap: 5.5 Identified at PRAPeR 63 meeting. Applicant to further address the risk to aquatic insects.			PRAPeR 63 (13 – 15 January 2009) Data gap open. Written procedure Data gap remains open.
	Open point 5.6 RMS to recalculate in an addendum the TERs for	Notifier: Some clarification is needed. For the calculation of refined long-term TERs for pyriproxyfen, a FOCUS Step	December 2008: The corrected Step 3 PECsw is only marginally different from the one	PRAPeR 63 (13 – 15 January 2009) Open point open.

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	aquatic organisms with the corrected PECsw. See reporting table 5(18)	3 surface water PEC value of 0.393 µg a.s./L has been used. The drift value for this is 2.77% (over 1.3 m, the standard distance to the crop in Step 3, D6, ditch). However, reference is made to 1.6, which is the aeric mean mass deposition, expressed as percentage of the application rate The PEC value is also inconsistent with that calculated in the Fate and Behaviour section i.e. 0.381 µg a.s./L (Table 2.5.3-14). This needs to be standardised (this change does not influence the outcome of the risk assessment)	presented in the DAR (0.393 vs. 0.381 ug a.s./L). The TER values calculated with this PECsw (TERlt for fish and *Daphnia*) do not change as a result of the correction (they remain 11 and 13, respectively). Therefore, we have not presented the corrected TER values in the addendum. However, the correct value is now mentioned in the LoEP (December 2008), and we will address this in the revised DAR. February 2009: This has been done. Note that more changes have been made in the revised Vol. 3 of the DAR in several sections. These are all minor changes which were mentioned in the reporting table but not taken to the evaluation table. All changes are marked in red. NB Vol.1 of the DAR has **not** been revised.	RMS to revise the DAR. Written procedure Open point fulfilled RMS has updated the DAR with corrected PECsw values.
	Open point 5.7 RMS to delete the LD50 values for bees from studies which are considered not acceptable See reporting table 5(22)	Notifier: According to the 5 batch analysis and the specification defined in the dossier (Document J Specification No. 01), the test material used in the honey bee acute toxicity study by Hoberg J.R. (2001) is in the range of technical grade pyriproxyfen and so the study should be valid. Further studies are not needed since acceptable data for the toxicity of the formulation to	December 2008: The specification overview provided by the notifier and presented in Vol. 4-Addendum Ecotox (December 2008) states that the tested batch in this bee toxicity study was batch no. 00303 with purity 987 g/kg. The study report itself however mentions batch no. 00303G with purity 99.7%. Since this contradiction still needs clarification, the	PRAPeR 63 (13 – 15 January 2009) Open point fulfilled.

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		honey bees are available	endpoints from the study on bees with the active substance have been deleted from the LoEP and the list of studies relied upon. Further studies are not required since the risk assessment can be performed with the endpoints from the study with the formulation.	
	Data gap: 5.1 Applicant to address the risk to bee brood for the use in tomato and egg plant in Southern EU.	Notifier: Accepts that the risk to bee brood for the use in tomato and egg plant in southern EU needs to be addressed either by generating appropriate data or by including a warning phrase on the label. The Notifier also agrees with the RMS that this should be addressed at Member State level in order to take into account local practice e.g. use of bumble bees in glasshouse pollination, and to conform with national risk management procedures and associated label phrases	December 2008: This issue will be addressed at MS level. No action required.	PRAPeR 63 (13 – 15 January 2009) Data gap open. Further studies are necessary for SEU greenhouse use in tomato and eggplant Written procedure Data gap remains open
	Open point 5.8 MSs to discuss in an expert meeting the ER50 calculation for A. rhopalosiphi. See reporting table 5(30)	Notifier: In the Tier 1 laboratory study with A. rhopalosiphi, since the lowest dose (31.25 g a.s./ha) is lower than the NOER (62.5 g a.s./ha) and thus outside the dose-effect relationship range (62.5-125 g a.s./ha), this rate should not be included in the regression analysis for the ER50 evaluation. Based on this, an ER50 value of 92 g a.s./ha would be more appropriate	December 2008: We considered that the possibility cannot be excluded that the effect seen at the lowest dose is treatment related. Therefore we included the lowest dose rate in the calculation of the ER50. It should be noted that the outcome of this discussion on the risk assessment is low, since the difference between the two ER50-values is small (92 vs. 81 g a.s./ha) and *A. rhopalosiphi* is not the	PRAPeR 63 (13 – 15 January 2009) Open point fulfilled.

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			most sensitive species.	
	Open point 5.9 RMS to check and revise the HQ values for A. rhopalosiphi and Orius laevigatus in a revised DAR. See reporting table 5(31)	Notifier: In Table 2.6.3.2-2, the sublethal HQ values of 0.93, 3E-4, <0.17 and 5E-5 should not be in bold (as in Table B.9.42). The off crop HQ values (1 m) for *Aphidius rhopalosiphi* and *Orius laevigatus* need to be corrected in both tables (the calculation has divided by the uncertainty factor of 10 rather than multiplied)	December 2008: Values will be checked and revised if necessary when we revise the DAR. February 2009: Vol.1 has not been revised. However, in the revised Vol.3 and the revised LoE, the off-crop HQ-values have been corrected. The standard format of the LoE has been used. Proposal: open point closed.	PRAPeR 63 (13 – 15 January 2009) Open point open. RMS to update the LoE and to use the standard format and revise DAR on this issue Written procedure Open point fulfilled
	Open point 5.10 MSs to discuss in an expert meeting whether the risk to non-target arthropods is sufficiently addressed considering the particular mode of action of pyriporxyfen. See reporting table 5(32)	Notifier: Agrees with the RMS that the non-target arthropod risk assessment for pyriproxyfen specifically takes into account its IGR mode of action according to the guidance provided in ESCORT 2. Thus, Tier 1 (glass plate) tests were conducted with *T. pyri* and *O. laevigatus* in order to ensure exposure of appropriate juvenile stages (a study with *A. rhopalosiphi* is also provided). An assessment is presented using both mortality and sublethal (reproductive) parameters, again taking into account the IGR mode of action. A reduced HQ trigger of 1 is used, which relates to the recommended 50% effect threshold. An acceptable off-field risk is identified for all uses and this is also the case for the in-field risk except with *T. pyri*. Accordingly, extended lab. tests	December 2008: In the risk assessment, we have followed the guidance for IGRs recommended in Escort 2 (trigger of 50% effect is equal to HQ of 1). We agree that the appropriateness of this guidance could be discussed in an Expert Meeting (e.g. should tests cover the full lifecycle and not just a part?), but in our view the discussion should have a broader context and not be just about pyriproxyfen.	PRAPeR 63 (13 – 15 January 2009) Open point fulfilled.

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		were conducted for *T. pyri* and *Chrysoperla carnea* which demonstrate an acceptable in-field risk for all uses with fresh, dried residues (0 d ageing)		
	Data gap: 5.2 Applicant to submit the studies on effects of technical pyriproxyfen on soil respiration and nitrification. See reporting table 5(33)	Notifier: A new GLP study (NNW-0178) to assess the effects of technical pyriproxyfen on soil respiration and nitrification according to OECD 216 and 217 guidelines has been conducted and was submitted to the RMS in January 2006 (no adverse effects were detected on soil microbial respiration and nitrification at 1.5 mg a.s./kg soil, the highest concentration tested). The RMS has acknowledged the receipt of this study, which will be included in an addendum	December 2008: The new study is included in the addendum, the LoEP and the list of studies relied upon (all from December 2008). The results indicate low risk for soil respiration and nitrification. February 2009: New data could not be taken into account because of Regulation 1095/2007, but please note that a new study was submitted, evaluated in the addendum, and found to be acceptable by RMS.	PRAPeR 63 (13 – 15 January 2009) Data gap open. Written procedure Data gap remains open. Please note that a new soil respiration and nitrification study was submitted, evaluated in the addendum, and found to be acceptable by RMS.
	Data gap: 5.3 The new study Report No. NNW-0178) submitted in January 2006 should be evaluated in an addendum. See reporting table 5(34)	Notifier: According to reporting table 5(34) this is an Open Point not a Data Gap (see previous point)	December 2008: Fulfilled, see above. February 2009: The new study was evaluated in the addendum, so this point should be closed. See also Data gap 5.2.	PRAPeR 63 (13 – 15 January 2009) Data gap open. Written procedure Open point fulfilled The assessment of the micro-organism in an addendum by RMS should have been considered as an open point in the first place and not as a data gap. As RMS has provided the addendum the, the open point is fulfilled.

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				See also data gap 5.2
	Open point 5.11 RMS to use the EPCO No E 4, revision 4 (September 2005) template for the list of endpoints when the LoEP is revised. See reporting table 5(37)		December 2008: This has been done to the extent that it was practically feasible. Not all TER calculations are in the new format. However, all required information is presented. February 2009: The correct template has now been used. Proposal: open point closed.	PRAPeR 63 (13 – 15 January 2009) Open point open. RMS to update the LoE, according to the EPCO No E 4, revision 4 (September 2005) template. Written procedure Open point fulfilled
	Data gap: 5.4 Applicant to provide specifications of Pyriproxyfen 100 g/L and Pyriproxyfen 10% EC, and submit an assessment of the compliance of the used materials (different batches of active substance) with the specification of the technical material. See reporting table 5(39)	Notifier: Details of the specifications of the formulations used and the compliance of the used materials (different batches of active substance) with the specification of the technical material was submitted to the EFSA by the agreed deadline of 01 December 2007	December 2008: The information provided by the notifier has been included in Addendum Vol.4-Ecotox (December 2008).	PRAPeR 63 (13 – 15 January 2009) Data gap turned into a point of clarification. Point of clarification addressed.