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0. General

General				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
0(1)	List of studies relied on version 1 November 2005.	EFSA: The list should be amended as it is currently not reliable for example Kimura, M. 2000a,b,c could not be found in the DAR.	RMS: In the DAR in section B.2.1. the reference Kimura, 1989 in B.2.1.7, B.2.1.8 and B.2.1.9 should be replaced by Kimura, 2000b, Kimura, 2000a and Kimura, 2000c, respectively. This will be amended in the revised DAR.	Addressed: Rapporteur to consider in a revised DAR or corrigendum.

1. Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis

Identity (B.1, Annex C)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(1)	Vol 1, LOEP	EFSA: there is a new 2006 FAO specification and the end points should be amended accordingly and in line with EPCO manual E4.	RMS: LOEP has been amended.	Open point: The agreed template for the list of endpoints should be used.
1(2)	Vol. 1, Level 4, 4.1 Identity of the active substance (page 145)	Notifier: 'See 4.5' should read 'Sufficient information is submitted'.	RMS: Agreed that under point 4.5 no data regarding the identity of pyriproxyfen is requested. However, (new) data requirements have been identified regarding the identity of the active substance.	Data gap: : 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 also 1(8), 1(9), 1(10), 1(11)
1(3)	Vol. 4, C.1.1.2 starting materials	AT: The commercial availability of the starting materials (especially number 1) should be reported.	RMS: Agreed. This information will be included in an addendum to volume 4. The information is not available and therefore the NOT is requested to submit this data.	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 also 1(4)

Rapporteur:

Identity (B.1, Annex C)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(4)	Vol 4, C.1..1.2, starting materials	EFSA: Is the starting material [redacted] commercially available. If not then a specification and method of manufacture should be provided.	RMS: Agreed. The NOT will need to elaborate, since this information is not available in the dossier.	See point of clarification in comment 1(3)
1(5)	Vol 4, C.1.2, detailed specification of the active substance	UK: We consider that the specification needs amending with [redacted]	RMS: If the mean + 3xSD rule is used the following results are found: [redacted] However, since the footnote mentions the LOQ is not validated below 0.1%w/w, the data in the table is unreliable. NL is of the opinion these should be changed into < 0.1%. Therefore, NL agrees with the UK that both substances should be removed from the specification. The specification should be amended and volume 4 should be revised. This issue may be best addressed in an expert meeting.	Point of clarification for the applicant: [redacted] and therefore if they are not relevant impurities they should be removed from the specification. See also 1(7).
1(6)	Vol 4, C.1.2.2, isomers	EFSA: From the statement it is not clear if there is any data to demonstrate the biological activity of the isomers. This should be addressed.	RMS: There is no data to support the claim in volume 4 that there is no difference in biological activity between the two isomers of pyriproxyfen.	Data gap: 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.

Rapporteur:

Identity (B.1, Annex C)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(7)	Vol 4, C.1.2.3, specification	EFSA: From the 5 batch data the proposed specification for [redacted] is not justified.	RMS: Please refer to 1(5).	See point of clarification under comment 1(5)
1(8)	Vol. 4, Annex C, C.1.5, Additional information required to be submitted by the notifier	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.	RMS: The study has been received. The study will be included in an addendum.	See data gap under comment 1(2).
1(9)	Vol. 4, C.1.5 confirmation of one impurity by MS	AT: Is the study completed yet?	RMS: The study has been received. The study will be included in an addendum.	See data gap under comment 1(2).
1(10)	Vol 4, C.1.5, additional data required	UK: We agree with the data requirement for a confirmatory method (with accompanying validation data) for the method of analysis for the determination of [redacted] in technical material	RMS: The study has been received. The study will be included in an addendum.	See data gap under comment 1(2).
1(11)	Vol. 4, Annex C, C.3, References relied on	Notifier: Please add the report of NNA-0097 newly submitted for confirmation of the identity of Impurity #2 in the reference list.	RMS: The study has been received. The study will be included in an addendum.	See data gap under comment 1(2).

Physical and chemical properties of the active substance (B.2.1)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(12)	Vol. 1, Level 2, 2.1.2 Physical and chemical properties (page 13)	Notifier: The new GLP studies for relative density, spectra (IR, ^{1}H-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.	RMS: The study has been received. The study will be included in an addendum.	Data gap: GLP studies for relative density, spectra (IR, ^{1}H-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 also 1(13), 1(14), 1(15), 1(18), 1(19), 1(20), 1(21, 1(22), 1(24) and 1(25).
1(13)	Vol. 1, Level 2, Appendix 3, List of endpoints, relative density (page 94) Vol. 3, Table B.2.1, B.2.1.4 relative density	Notifier: A new GLP study (NNP-0102) was submitted to the RMS in January 2006. The relative density was measured using the air comparison pycnometer method (OECD 109). The result is as follows; D_4^{20} = 1143 kg/m^3	RMS: The study has been received. The study will be included in an addendum.	See data gap in comment 1(12)
1(14)	Vol 3, B..2.1.4, relative density	EFSA: We agree that a new density method is required.	RMS: The study has been received. The study will be included in an addendum.	See data gap in comment 1(12)

Physical and chemical properties of the active substance (B.2.1)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(15)	Vol 3 , B.2.1.4 relative density and B.2.1.10, spectra	UK: Data requirements for relative density and spectra (1 and 2 in vol 1 4.2) seem a bit harsh as only reason for rejection is they were not carried out to GLP.	RMS: New studies have been provided by the notifier. NL regards this comment addressed.	See data gap in comment 1(12)
1(16)	Vol 3, B.2.1.5, vapour pressure	EFSA: It is not understood why the vapour pressure has been accepted without a purity. Also it is not clear what is meant by the statement in the comments column. This should be explained	RMS: Agreed this statement could use some elaboration. The report mentions a lot no. and indicated that this is a pure active ingredient. Exact purity is unknown. Actually, the value stated in B2 is not correct. The report states a vapour pressure of $< 1.0 \times 10^{-7}$ Pa at 22.81 ^{o}C. Due to limitations of the test method, an exact value is not available. NL is unsure how the value of 1.33×10^{-5} Pa got into the DAR. The DAR should be corrected. As an answer to the question issued by EFSA NL would like to state that the vapour pressure of the test material (and therefore its individual components included) was too low to measure and therefore a statement that the test substance is 'pure' is considered acceptable.	Open point: Rapporteur should clarify what the correct vapour pressure is.

Physical and chemical properties of the active substance (B.2.1)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(17)	Vol 3, B.2.1.6,Henry's law	EFSA: A new calculation will be required when the new water solubility study is provided.	RMS: Agreed. A calculation of Henry's law constant should be included in an addendum to the DAR, based on data of the new water solubility study. (The new calculation should take into account tat the vapour pressure is incorrectly stated in B2 (see 1(16)). The available report makes use of the right values)	Data gap: 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.
1(18)	Vol. 3, Table B.2.1, B.2.1.10 spectra	Notifier: A new GLP study (NNP-0104) was submitted to the RMS in January 2006. The study includes IR, ^{1}H-NMR and Mass spectra to confirm the spectroscopic properties of pyriproxyfen.	RMS: The study has been received. The results will be included in an addendum to the DAR.	See data gap in comment 1(12)
1(19)	Vol 3, B.2.1.10, spectra	EFSA: We agree that new spectra are required.	RMS: A study has been received. The results will be included in an addendum to the DAR.	See data gap in comment 1(12)
1(20)	Vol. 1, Level 2, Appendix 3, List of endpoints, solubility in water (page 95) Vol. 3, Table B.2.1, B.2.1.11 solubility in water	Notifier: A new GLP study (NNP-0105) was submitted to the RMS in January 2006. The water solubility was measured at different pHs using the column elution method (OECD 105). The results are as follows; Water solubility at 20±0.5°C = 0.058 mg/L at pH5 0.101 mg/L at pH 7	RMS: A study has been received. The results will be included in an addendum to the DAR.	See data gap in comment 1(12)

Rapporteur:

Physical and chemical properties of the active substance (B.2.1)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		0.119 mg/L at pH 9 These data indicate that the water solubility is independent of pH in the environmental range.		
1(21)	Vol 3, B.2.1.11, solubility in water	EFSA: We agree that a new study on solubility in water is required.	RMS: A study has been received. The results will be included in an addendum to the DAR.	See data gap in comment 1(12)
1(22)	Vol 3, B.2.1.11, solubility in water and B.2.1.13, partition coefficient	UK: With regards to these sections (3 and 4 in vol 1 4.2) we would agree with a data requirement being set.	RMS: Studies have been received. The results will be included in an addendum to the DAR.	See data gap in comment 1(12)
1(23)	Vol 3, B.1.12, solubility in organic solvents	EFSA: Further details of the test method should be provided.	RMS: Agreed. The method is a quite inaccurate screening method which comprises of two steps. The first step is a rough estimation of the solubility range of the test substance in a certain solvent. The refined test can be described as follows: a small amount of test substance is added to a solvent after which a visual check is performed on whether solubility was comlpete. The specified solubility range (e.g. 25 to 29 g/L in methanol) is the highest concentration at which solubility was complete and the lowest value at which solubility was *in*complete. > 1000 g/L means complete miscibility of the a.i. with the solvent. The DAR mentions a 'direct addition' technique which in essence is a correct description of the test method.	Addressed: The method is considered acceptable.

Physical and chemical properties of the active substance (B.2.1)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(24)	Vol. 1, Level 2, Appendix 3, List of endpoints, partition co-efficient (page 95) Vol. 3, Table B.2.1, B.2.1.13 partition coefficient	Notifier: A new GLP study (NNP-0103) was submitted to the RMS in January 2006. The *n*-octanol/water partition coefficient was measured at different pHs using the HPLC method (OECD 117). The results are as follows; Log Pow = 4.85 at pH5 4.86 at pH 7 4.87 at pH 9 These data indicate that the partition coefficient is independent of pH in the environmental range.	RMS: A study has been received. The results will be included in an addendum to the DAR.	See data gap in comment 1(12)
1(25)	Vol 3, B.2.1.13	EFSA: We agree that a new study for partition coefficient is required to investigate the effect of pH.	RMS: A study has been received. The results will be included in an addendum to the DAR.	See data gap in comment 1(12)

Physical and chemical properties of the active substance (B.2.1)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(26)	Vol 3, B.2.1.16, photochemical degradation	EFSA: It is not clear why this study has been accepted given that it used pyrex glass.	RMS: Agreed the comment is in need of elaboration. A screening test was performed, comparing exposure with and without a pyrex glass plate in comparison to natural sunlight. After the study was finished, another comparison with and without pyrex glass was performed. A clear graph, (appendix C of the report; showing exposure to natural sunlight, artificial light through pyrex glass and direct artificial light in one figure) is included in the report showing no significant difference in exposure with and without pyrex glass. NL therefore considers the study to be acceptable.	Addressed: Rapporteur to consider in a revised DAR or corrigendum.
1(27)	Vol 3, B.2.1.19, stability in air Atkinson calculation.	EFSA: Why is the value calculated by the RMS and not by the company. If it has been calculated by the RMS what are the references for.	RMS: In the comment column the data based on a 12h day provided by the NOT is stated, for which a reference is required. A 24 hour day calculation by the RMS is included in the results column. Data should have been switched around.	Addressed: The rapporteur has explained the situation.

Physical and chemical properties of the active substance (B.2.1)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(28)	Vol 3, B.2.1.22 and 23 explosive and oxidising properties.	EFSA: Some further information on the structural case that was presented by the applicant would be helpful.	RMS: Only the structure of the active substance was evaluated based on the absence of groups known to cause explosive behaviour. In combination with a DSC analysis of the technical material, which showed no high exothermal degradation takes place when heated to 600 ^{o}C, the RMS regards this information sufficient. Regarding the oxidising properties only the structure of the active substance was taken into account (oxygen balance and reactive groups). The report based its conclusion on a DSC analysis as well, although the relevancy of this data is questionable. None of the impurities included on the specification of pyriproxyfen have groups that would indicate oxidising potential.	Addressed: Rapporteur to consider in a revised DAR or corrigendum.

Physical and chemical properties of the active substance (B.2.1)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(29)	Vol. 2, A.2 Physical and chemical properties Vol. 3, B.2.3 References relied on	Notifier: The following four new studies submitted to the RMS in January 2006 should be added in the reference lists; - 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)	RMS: These modifications will be included in an addendum to the DAR.	Open point: 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.

Physical, chemical and technical properties of the formulation (B.2.2)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(30)	Vol 3, B.2.2, general	EFSA: 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.	RMS: Agreed. An awkward mistake. The table needs to be revised.	Open point 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.
1(31)	Vol. 3, B.2.2.5 oxidising properties	AT: The result given under 2.9.1 “physical compatibility with other products” (reactions with granular zinc and KMnO4) does not address this Annex point. A test according to EEC/A17 is required.	RMS: The NOT mentions in doc M-III no test is available for liquids, which is not acceptable. NL agrees with AT that a test according to EC A21 is required, unless a reasoned statement, based on the individual components of the formulation is submitted.	Point of clarification for the applicant: The oxidising properties of the formulation needs to be addressed. See also 1(32).
1(32)	Vol 3, B.2.2.5, oxidising properties	EFSA: Some further details of the case that was made by the applicant would be helpful.	RMS: Please refer to 1(31). A new study or reasoned statement is required.	See point of clarification in comment 1(31)
1(33)	Vol 3, B.2.2.15, shelf life	EFSA: The container material should be given.	RMS: Agreed. The report mentions PE/PB co-extruded bottles, which is equal to the packaging proposed for commercial use (see B.3, further information on the ppp).	Open point: 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.
1(34)	Vol. 3, 2.9.1 physical compatibility	AT: The statement given does not cover physical compatibility.	RMS: An awkward mistake. This information does not belong here. Mixing of the product is however not proposed. No additional data is required. The table should be revised.	Addressed: Compatibilities are not requested. See also 1(35)

Rapporteur:

Physical, chemical and technical properties of the formulation (B.2.2)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(35)	Vol 3, B.2.9.1, compatibility with other products.	EFSA: It is not clear what EPA 63-14 is for when in the box below it states that mixing with other products is not required.	RMS: Please refer to 1(34). No test is available and therefore mentioning of a method is not appropriate. The table should be revised.	See comment 1(34).
1(36)	Vol 3, B.4.2, classification and labelling of preparations, physical chemical properties	UK: the statement at B.4.2 is incorrect, surface tension data indicate the need for a R65 (as stated in the Tox section) and S62 risk phrases.	RMS: Agreed the statement is incorrect. For a measurement at 40 °C the threshold is 25 mN/m, which is not exceeded. At 25 °C the threshold is 33 mN/m. No threshold is set at 20 °C. Based on the above, the measurement at 40 °C should be used for consideration of labelling with R65. Although just barely so, the trigger of 25 mN/m at 40 °C is not met. Thus, based on physical and chemical properties, labelling with R65 is not required. R65 should therefore be removed from the proposal for labelling (the notifier did not include R65 in the proposal for classification and labelling of the preparation). If desired, this point should be discussed in an expert meeting.	Open point: The need for R65 classification should be discussed by a meeting of experts.

Classification and labelling (B.4)

For comments on classification and labelling see the relevant sections.

Rapporteur:

Methods of analysis (B.5)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
1(37)	Vol. 1, List of endpoints	DE: Remark: "The Definition of the Residue: (Annex IIA, point 7.3) Relevant to the environment" on page 134 differs from Vol. 1, 2.5.1. Please add a note in List of endpoints that metabolites are not relevant for monitoring. On the other hand, if for monitoring metabolites have to be included, please change chapter 2.5.1. In the last case, methods for metabolites are missing.	RMS: The residue definition for monitoring purposes in the environment is identified as pyriproxyfen (page 154). The definition of the residue mentioned in volume 1, 2.5.1, is incorrect. The DAR will be corrected.	Addressed: Rapporteur to consider in a revised DAR or corrigendum.
1(38)	Vol. 3, B.5.2 anal. methods in plants	AT: More information concerning linearity is requested as it seems that linearity data are not in accordance with guidance document SANCO 825/00 (one point calibration) and the determined recoveries therefore in doubt.	RMS: In the validation report of method DFG S19 for determination of pyriproxyfen in cucumber it is mentioned a one point calibration was carried out. NL believes the linearity to be sufficiently displayed, because linearity is based on a calibration of 7 solutions with a concentration range of 0.010 to 1.33µg/L (r^2 = 0.9990).	See data gap in comment 1(40).
1(39)	Vol. 1, 2.2 and Vol. 3, B.5.2	DE: Remark: A clear conclusion on the suitability of additional MS traces to confirm positive findings is missing.	RMS: Please refer to 1(40).	See data gap in comment 1(40).
1(40)	Vol 3, B.5.2, plant methods	EFSA: At the most only two acceptable ions above 100 have been monitored therefore confirmatory methods are required. In addition to this as more than one crop is covered by the representative uses then all of the matrix groups should be validated.	RMS: The modified DFG-S19 method for plant material, validated for cucumber, makes use of 3 mass fragments. However, one of those mass fragments (136 for quantitation, 78 and 226 for confirmation) is not > 100 m/z. The method validated for cotton seed does not make use of the 226 m/z ion for confirmation. Only two mass fragments were used, which is insufficient.	Data gap: The need for a method of analysis for plants including ILV and a confirmatory method if necessary. has been identified. See also 1(38), 1(39)

Rapporteur:

Methods of analysis (B.5)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
			NL agrees with EFSA that for every matrix type a full validation, including confirmatory methods and ILV's are required. Based on the above, an ILV and confirmatory method should be provided for the residue analytical method for determination of residues of pyriproxyfen in cotton. NL regards validation of the method for commodities with a high water content sufficient. If necessary, the acceptability of the 78 m/z ion for confirmatory purposes should be discusses in an expert meeting.	
1(41)	Vol. 1, 2.2 and Vol. 3, B.5.3	DE: Remark: Except from the method for residues in air a clear conclusion on the suitability of additional MS traces to confirm positive findings is missing.	RMS: For studies 1, 2 and 3 (methods for soil and water) in B.5.3 is stated sufficient mass-fragments were used for confirmation purposes. This is indeed not included in the summary in volume 1. If so desired, NL will amend the summary to include the method is considered sufficiently specific based on the use of >3 >100 m/z mass fragments.	Addressed: Rapporteur to consider in a revised DAR or corrigendum.
1(42)	Vol 3, B.5.3, soil and water methods.	EFSA: The validation for the GC-MS confirmatory methods should be given.	RMS: Agreed. Validation is missing. Data will be included in an addendum to the DAR. NL confirms data is available in the study reports provided by the NOT.	Open point: 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.

Rapporteur:

Comments received on reporting table, section Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis (B.1- B.5)			
Reference to reporting table	MS / Notifier	Comment	EFSA response
1(2)	NOT	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 which will be included in an addendum.	Noted
1(3)	NOT	The required information will be provided. Proposed submission date: 01 December 2007.	Noted
1(5)	NOT	The Notifier's position about these impurities will be provided. Proposed submission date: 01 December 2007.	Noted
1(6)	NOT	Information to support the biological activity of the isomers will be provided. Proposed submission date: 01 December 2007.	Noted.
1(12)	NOT	The 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 which will be included in an addendum.	Noted
1(16)	NOT	Notifier believes that RMS could mistakenly revise the vapour pressure of <1.33 x 10-5 Pa as shown in the 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 22.81 ^{o}C, hence the correct value should be <1.33 x 10 -5 Pa as indicated in the DAR. Based on the 1(17) of the current table, notifier will submit the new report of Henry's law constant in which the correct vapour pressure (<1.33 x 10-5 Pa) is used for the calculation.	Noted
1(17)	NOT	The RMS has acknowledged the receipt of the new study for water solubility and a new calculation of Henry's Law constant can be included in an addendum. A study confirming the new Henry's Law Constant will be provided. Proposed submission date: 01 December 2007	Noted

Rapporteur:

Comments received on reporting table, section Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis (B.1- B.5)			
Reference to reporting table	MS / Notifier	Comment	EFSA response
1(31)	NOT	EEC A17 study guideline is exclusively dealing with solid products. Pyriproxyfen 10 EC is a liquid product, so the requested study cannot be conducted following the proposed study guideline. The Notifier believes that the available study following US EPA study guidelines is fully valid to supports the EU requirement for oxidising properties of a liquid product like Pyriproxyfen 10 EC.	Noted changed to A21
1(33)	NL	The material PE/PB is not specified in dossier; the summary document includes the same text as submitted in the packaging specification in the KIII document. The 0.25L container is made out of this material. Based on personal experience, PB is probably polybutadiene which can be copolymerised with ethylene to give a more flexible plastic. It seems PE was co-extruded with 2.5% PE/PB copolymer. The PE/EVOH container should be separately tested, but a shelf-life study is not available. NL would suggest leaving this for MS level product authorisations because this data is not quite relevant for annex I inclusion of the active substance.	Noted
1(36)	NOT	The Notifier agrees with the UK and the RMS that R65 is not required based on the trigger for surface tension not being reached.	Noted
1(40)	NOT	The Notifier requests clarification as to which plant matrices are being discussed and what additional validation is necessary. In the reporting table the RMS considers the plant method for high water containing matrices to be adequate since quantification has been performed using m/z 136 and verification using m/z 78 and 226. Even though one of the verification ions is below 100, it is considered suitable methodology is available. Reasoned arguments are presented in the ILV report (Study 2) as to why a verification ion <100 was chosen and chromatography within the report shows m/z 78 could be used for verification if required. 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. Therefore the 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 with quantification using m/z 136. ILV of this method (Study 4) shows successful validation on olives again using ion m/z 136 for quantification.	Noted

Rapporteur:

Comments received on reporting table, section Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis (B.1- B.5)			
Reference to reporting table	MS / Notifier	Comment	EFSA response
		Therefore in terms of primary methodology a suitable validation of a method for commodities with high fat content has been adequately demonstrated. For confirmatory analysis, ion m/z 78 was proposed during the original validation but ion m/z 226 was not indicated. However, since the ILV was performed by the same laboratory who generated Study 2, an assessment was made again using both ions m/z 78 and 226 for verification and again reasoned arguments are presented in the report (Study 4) as to the use of an ion with m/z <100 and the suitability of ions m/z 78 and 226 as verification ions. Therefore sufficient information is also considered to have been submitted for analysis of crops with high fat content. In the meantime, according to the EU commission recommendation in the Official Journal of the European Union, L 19/23, 24.1.2006, a monitoring programme for pyriproxyfen in several crops has already started in 2007, and the target 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 authorities. In addition, a new MRM using LC/MS/MS has already developed in Germany and pyriproxyfen is the one of pesticides for which the LC/MS/MS methods can be applicable (See the following web sites: www.bfr.bund.de/cd/5832 , and www.bfr.bund.de/cm/218/liste_der_pestizide_zu_denen_gegenwaertig_methodische_informationen_verfuegbar_sind.pdf) Since the official MRMs are available for pyriproxyfen in several crops in EU, it seems that any further validation for DFG-S19 is less useful. Confirmation is therefore requested as to whether further validation is necessary.	

Comments received on reporting table, section Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis (B.1- B.5)			
Reference to reporting table	MS / Notifier	Comment	EFSA response
1(40)	NL	It is unclear what EFSA thinks of the linearity issue, discussed under 1(38). If the linearity of the method is acceptable and the confirmatory technique based on 3 mass fragments, one of which is < 100 m/z, is acceptable, then no new method for matrices with a high water content is required. NL is of the opinion that only for cotton a confirmatory method and ILV are required. The data requirement under 1(40) seems to suggest that for all matrices new validated methods are required. If this is the case, please confirm. Perhaps acceptability of the method for cucumber should be discussed in an expert meeting.	Noted

2. Mammalian toxicology

Toxicokinetics (B.6.1)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(1)	Vol.1, Level 2, 2.3.1.1 Toxicokinetics, Absorption Vol. 1, Level 2, Appendix 3, Rate and extent of absorption Vol. 3, B.6.1 Absorption, distribution, excretion and metabolism (Absorption rate)	Notifier: Pages 17, and 102 (Vol.1) and pages 57, 70, 144, and 155 (Vol.3): Notifier considers that the oral absorption rate of 63% proposed in the dossier is already a worst case estimate. 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 same range is quoted based on urine, CO_2, tissues, cage wash, residual carcass and bile. The values used to calculate absorption and the	RMS: The amount of unchanged pyriproxyfen in the faces is considered the minimum unabsorbed dose. However, the metabolic profiles of the bile and faeces are not comparable, e.g. one of the major metabolites found in faeces (4'-OH-pyriproxyfen) was not found in bile. Therefore, it cannot be excluded that metabolism of pyriproxyfen occurs in the intestines. In absence of further data, which exclude the possibility of metabolism in the intestines, a worst-case assumption for oral absorption should be made. Based on these considerations it is concluded that the oral absorption should be based on the amount of radiolabel found in bile, urine, tissues, cage wash and carcass, as found in the ADME study of Isobe (1988a). The results of this study indicate that after a single dose of 2 or 1000 mg/kg bw pyriproxyfen, absorption amounts to 39-49% AR in males and females. For risk assessment purposes, 40% oral absorption is taken as a worst-case	Open point RMS to provide more details on the study of Isobe (1988a) to clarify the calculation of oral absorption. Open point (RMS's proposal) Oral absorption value to be discussed by the experts.

Toxicokinetics (B.6.1)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		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-^{14}C]pyriproxyfen or [pyridyl-2,6-^{14}C]pyriproxyfen, and it was decreased to	estimate.	

Toxicokinetics (B.6.1)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		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. Page 17 4th paragraph 1st sentence (Vol.1), page 102 (Vol.1), page 57 3rd paragraph 2nd sentence (Vol.3), page 70 1st paragraph 1st sentence (Vol.3) and page 144 2nd paragraph 1st sentence (Vol.3): Notifier considers that absorption was ca. 63% of the applied dose, based on the metabolites excreted in the urine, faeces, expired CO_2, tissues, cage wash and residual carcass. Page 18 1st paragraph (Vol.1), page 70 3rd paragraph (Vol.3) and page 144 4th paragraph (Vol.3): Notifier considers that for risk assessment purposes, 63% oral absorption is taken as a worst-case estimate. Therefore, the section of absorption in page 17		

Toxicokinetics (B.6.1)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		(Vol.1), page 70 (Vol.3) and page144 (Vol.3) should be changed as follows: As unchanged pyriproxyfen was not eliminated in bile in biliary excretion study, it was considered that the pyriproxfen in faeces of normal rats is unabsorbed compounds whereas the metabolites in faeces of normal rats are absorbed compounds. Based on this finding, the absorption was determined to be ca. 63% of the applied dose after single (2 or 1000 mg/kg) administration of [phenoxyphenyl-^{14}C] pyriproxyfen or [pyridyl-2,6-^{14}C] pyriproxyfen to rats, since 21-37.2% of the applied dose in faeces was unabsorbed pyriproxyfen. After repeated (2 mg/kg) oral administration of [phenoxyphenyl-^{14}C] pyriproxyfen, absorption was ca. 89% at minimum since faecal pyriproxyfen was 6.5 - 11.4%. In mice absorption after a single dose of 2 or 1000 mg/kg was ca. 75% AR at minimum since faecal pyriproxyfen was 12 - 25%. For risk assessment purposes, 63% oral absorption is taken as a worst-case estimate.		
2(2)	Vol. 3, B.6.1 Absorption, distribution, excretion and metabolism and B.6.1.4 Summary and conclusions	Notifier: Page 17 4th paragraph (Vol.1), page 57 3rd paragraph (Vol.3), page 70 1st paragraph (Vol.3) and page 144 2nd paragraph (Vol.3): Notifier does not believe there is any evidence for a first pass effect and suggests this should be changed. Notifier questions the conclusion concerning	RMS: Agree. Bile excretion was measured after 24 and 48 hours and indeed, based on the data, it cannot be concluded that there is a first pass metabolism. For example the sentence at page 57, 3rd paragraph (vol. 3) should read: 'Metabolites detected in the bile were shown to contribute substantially to the amount of	Addressed

Rapporteur:

Toxicokinetics (B.6.1)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		first pass metabolism. First pass metabolism is normally determined by measuring bioavailability following oral and intravenous administration, it is not clear how a conclusion concerning first pass metabolism has been determined from the data supplied. The use of the term first pass metabolism in this DAR may be inconsistent with the generally accepted definition of the term.	radioactivity excreted via the faeces.' This will be amended in a revised DAR (and has no further consequences with regard to the evaluation/conclusions).	

Short-term toxicity (B.6.3)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(3)	Vol. 1, Level 2, 2.3.1.2 Toxicodynamics, Short-term and semi-chronic toxicity Vol. 3, B.6.3.3 Subacute inhalation studies, STUDY 1 Vol. 3, B.6.3.5 Summary	Notifier: Page 21 4th paragraph (Vol.1), page 90, page 105 the last paragraph (Vol.3): Notifier considers that increased LDH and slight changes of some organs weights in male at 1000 mg/m^3 should be of little toxicological significance as described in the dossier (Document M-II) and the original report (Report No. NNT-80-0031). Therefore, Notifier thinks the description related to increased LDH, and changes of liver, spleen and lung weights in male at 1000 mg/m^3 should be deleted. Notifier strongly believes that increased LDH and slight changes of some organs weights in male at 1000 mg/m^3 should be considered of little toxicological significance. These	RMS: It is in general very difficult with these kind of effects to decide whether the effects are adverse or not. The individual effects are indeed not very strong, although absolute lung and spleen weights were decreased with more than 10%. Taking all the effects at 1000 mg/m^3 into account (salivation, increased LDH, decreased absolute lung weight, decreased absolute spleen weight and increased relative liver weight), the RMS considers the NOAEL of 482 mg/m^3 justified.	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. Open point 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.

Short-term toxicity (B.6.3)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		differences were marginal, showed no dose-dependency, were within physiological changes, and there were no related histopathological changes or no statistically significant changes.		
2(4)	Vol. 1, Level 2, 2.3.1.2 Toxicodynamics, Short-term and semi-chronic toxicity Vol. 3, B.6.3.4 Semichronic oral studies, STUDY 4 Vol. 3, B.6.3.5 Summary	Notifier: Page 23 1st paragraph (Vol.1), pages 103 1st paragraph, page 107 2nd paragraph (Vol.3): Notifier suggests that the sentence of "Based on higher cholesterol levels and higher liver weights the NOAEL is set at <30 mg/kg bw/d for males and 30 mg/kg bw/d for females" should be changed as follows, "Based on slightly higher cholesterol levels and slightly higher liver weights the NOAEL is set at <30 mg/kg bw/d for males and 30 mg/kg bw/d for females". Notifier considered that the changes of cholesterol levels and liver weights were slight or marginal in male at 30 mg/kg bw/d as described in the dossier (Document M-II) and the original report (Report No. NNT-11-0081).	RMS: Disagree. Cholesterol levels were 151% of control in males receiving 30 mg/kg bw/day, and absolute and relative liver weights were 130% and 129% of control, respectively. These are not considered 'slight' changes.	Open point 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.

Long-term toxicity and carcinogenicity (B.6.5)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(5)	Vol. 3, B.6.5.1 Chronic toxicity and carcinogenicity, STUDY 1	Notifier: Page 116 1st paragraph, page 119 1st paragraph (Vol.3): Notifier considers that this finding, "At post-mortem necropsy, an increased incidence of dark areas in the liver was noted in females at 3000 mg/kg food", was not treatment-related as described in the dossier (Document M-II) and the original report (Report No. NNT-11-0085 and NNT-41-0112). Therefore, Notifier thinks this sentence and the incidence of this finding in the table 6.5.1.1 should be deleted. An 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, Notifier considers that this finding was not treatment-related.	RMS: 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.	See open point in 2(6).
2(6)	Vol. 3, B.6.5.1 Chronic toxicity and carcinogenicity, STUDY 1	Notifier: Page 116 2nd paragraph (Vol.3), page 119 1st paragraph: "Treatment-related histopathological changes were noted in the liver at 3000 mg/kg food. A slightly increased incidence of liver necrosis was noted in males at 3000 mg/kg that died during the study. Liver necrosis was only noted in one	RMS: 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% and 25% for the males and females respectively in the 3000 mg/kg bw/d group. The RMS	Open point 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 also in 2(5), 2(7), 2(8).

Long-term toxicity and carcinogenicity (B.6.5)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		surviving animal at 600 mg/kg food." Notifier considers the sentences should be deleted, and the incidence of this finding in Table 6.5.1.1 should be also deleted. It was 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 as described in the dossier (Document M-II) or the original report (Report No. NNT-11-0085 and NNT-41-0112). Moreover, percent of the incidence of liver necrosis is 13% for males and 8% for females. These are within the range of historical data (0.0-24.0% for males, 0.0-18.0% for females).	considers this a relevant finding and does not agree with the notifier that this finding should be deleted from the DAR.	
2(7)	Vol. 3, B.6.5.1 Chronic toxicity and carcinogenicity, STUDY 1	Notifier: Page 116 3rd paragraph (Vol.3): Notifier suggests that the sentences of "Based on the decreased body weight gain the NOEL is set at 120 mg/kg food (equal to 5.4 mg/kg bw/day in males and 7.0 mg/kg bw/day in females). The NOAEL is set at 600 mg/kg food (equal to 27.2 mg/kg bw/day in males and 34.4 mg/kg bw/day in females)" should be changed to "Based on the decreased	RMS: the sentence "Based on the decreased body weight gain the NOEL is set at 120 mg/kg food (equal to 5.4 mg/kg bw/day in males and 7.0 mg/kg bw/day in females) can be deleted, since this is not very relevant for the conclusions of the study. To be amended in a revised DAR. The RMS will however not change the concluding sentence: 'The NOAEL is set at 600 mg/kg food, based on	See open point in 2(6).

Long-term toxicity and carcinogenicity (B.6.5)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		body weight gain the NOEL is set at 600 mg/kg food for males (27.31 mg/kg/day) and 120 mg/kg/day for females (7.04 mg/kg/day)". As recorded in Table 6.5.1.1 the decreased body weight gain was not observed in males given 600 mg/kg food.	changes in clinical biochemistry and increased liver weights and histopathological changes in the liver.'	
2(8)	Vol. 1, Level 2, 2.3.1.2 Toxicodynamics, Long-term toxicity Vol. 3, B.6.5.1 Chronic toxicity and carcinogenicity, STUDY 1 Vol. 3, B.6.5.2 Summary	Notifier: Page 23 4th paragraph (Vol.1), page 116 3rd paragraph, page 119 2nd paragraph (Vol.3): The histopathological changes were not considered to be treatment-related as mentioned in the comments provided under point No 2(6). Incidence of necrosis in the liver. Therefore, "and histopathological changes in the liver" should be deleted.	RMS: Disagree, see 2(6).	See open point in 2(6).
2(9)	Vol. 3, B.6.5.1 Chronic toxicity and carcinogenicity, STUDY 2	Notifier: Page 118 1st paragraph lines 5-6 (Vol.3): The slightly reduced body weight gain was not statistically significant and is not described in the dossier (Document M-II) or the original report (Report No. NNT-11-0084). Notifier considers that the effect was	RMS: This finding was observed, possibly treatment-related and thus described. This finding, however, does not trigger the derivation of the NOAEL. RMS still considers that this finding should be presented in the DAR.	Addressed.

Long-term toxicity and carcinogenicity (B.6.5)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		marginal and not necessarily treatment-related, therefore, this sentence, “A slightly reduced body weight gain was noted in females over the study period (0-76 weeks, 89% of control)”, should be deleted.		
2(10)	Vol. 1, Level 2, 2.3.1.2 Toxicodynamics, Long-term toxicity Vol. 3, B.6.5.1 Chronic toxicity and carcinogenicity, STUDY 2 Vol. 3, B.6.5.2 Summary	Notifier: Page 24 5th paragraph (Vol.1), page 118 the last paragraph, page 120 the last paragraph (Vol.3): Notifier considers that the NOAEL for females should be 600 mg/kg food as described in the dossier (Document M-II) and the original report (Report No. NNT-11-0085). “The NOAEL is set at 120 mg/kg food” should be changed to “the NOAEL is set at 120 mg/kg food for males (16.4 mg/kg bw/day) and 600 mg/kg food for females (107.3 mg/kg bw/day)”. There was no significant effect on either survival, liver weights or the incidence of histopathology changes in the kidney in female mice given 600 mg/kg (table 6.5.1.2). There is also no evidence of a significant increase in the incidence of amyloidosis in any tissue of female mice at this dose level.	RMS: The NOAEL of the study was based on the effects observed in males. These effects were indeed not observed in females at 600 mg/kg food. It is however common practice to derive an overall NOAEL for the study, based on the critical effects observed in the most sensitive sex (in case there is a difference in sensitivity between the sexes).	Addressed.

Long-term toxicity and carcinogenicity (B.6.5)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(11)	Vol. 1, Level 2, 2.3.1.2 Toxicodynamics, Long-term toxicity Vol. 3, B.6.5.2 Summary	Notifier: Page 24 3rd paragraph (Vol.1), page 119 2nd paragraph (Vol.3): The sentences of "At post-mortem necropsy, an increased incidence of dark areas in the liver was noted in females at 3000 mg/kg food. Treatment-related liver necrosis was noted in males at 3000 mg/kg food" should be deleted. Notifier considers that this finding was not treatment-related as described in the dossier (Document M-II) and the original report (Report No. NNT-11-0085 and NNT-41-0112). An increased incidence of dark areas in the liver was only noted in the main study but no histopathological changes related to this finding were observed. An increased incidence of liver necrosis was only noted in the animals that died before the end of the dosing period. It was generally secondary to some other cause of death and not treatment-related since no incidence of liver necrosis was noted at the scheduled sacrifice at week 53 and week 105 as described in the dossier (Document M-II) or the original report (Report No. NNT-11-0085 and NNT-41-0112).	RMS: see 2(5) and 2(6).	Addressed. See 2(5) and 2(6).

Reproductive toxicity (B.6.6)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(12)	Vol. 1, Level 2, 2.3.1.2 Toxicodynamics, Reproduction and developmental toxicity Vol. 1, Level 2, 2.3.2 Table 2.3.2.1 Vol. 3, B.6.6.1 Reproductive toxicity, STUDY 1 Vol. 3, B.6.6.3 Summary and Table 6.6.3.1	Notifier: Page 25 2nd paragraph, page 27 Table 2.3.2.1(Vol.1), page 124 2nd paragraph, page 139 Table 6.6.3.1, page 140 2nd paragraph (Vol.3): Notifier considers the NOAEL for parental toxicity was 1000 mg/kg food. The "Parental NOAEL=13.3; LOAEL=66.7" for 2-Generation, oral, rat in Vol. 1 (Level 4) should be changed to "Parental and developmental NOAEL=76.4 mg/kg ; LOAEL=386 mg/kg" A JMPR evaluation decided that the increase in relative liver weights in F1 males at 1000 mg/kg food was not adverse. 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. Our recommendation for achieved doses are as follows: 200 mg/kg food = 15.5 mg/kg bw/day 1000 mg/kg food = 76.4 mg/kg bw/day 5000 mg/kg food = 386 mg/kg bw/day Each value was calculated during the pre-mating period in each generation and by sex and group; the lowest values among them were selected.	RMS: See Vol. 3 of the DAR, B.6.6.1, STUDY 1, acceptability: "Histopathology was not performed on the livers of all animals of the 200 and 1000 mg/kg food groups. Based on this consideration and in the absence of clinical biochemistry, effects on liver weights were considered adverse for the establishment of the NOAEL." The RMS therefore still proposes a parental NOAEL of 200 mg/kg food. With regard to the food conversion from a dose level in mg/kg food to mg/kg bw/day: This is always difficult for a 2-generation reproduction study. In the study report no conclusions are drawn with regard to food conversion. At EPCO 14 in October 2004 in York it was decided to use the default food conversion factor of 15 in future assessments and therefore this factor of 15 was applied. It should furthermore be noted that the difference between the achieved dose levels in the DAR (13.3, 66.7 and 333.3 mg/kg bw/day) and those proposed by the notifier is not significant.	Open point 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). RMS could provide a revised table 6.6.1.1 with additional figures in order to ease the discussion.

Rapporteur:

Reproductive toxicity (B.6.6)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(13)	Vol. 3, B.6.6.1 Reproductive toxicity, STUDY 2	Notifier: Page 124 Characteristics (Vol.3): "Teratogenic effects: ≥ 1000 mg/kg bw/day" should be changed to "Teratogenic effects: Not teratogenic", because no teratogenicity was observed even in the highest dose level.	RMS: This is a matter of preference, the meaning of both sentences is in principle the same (mentioning the highest dose level provides more information to the reader). In the list of endpoints it is described as 'No teratogenic effects.'	Addressed.
2(14)	Vol. 3, B.6.6.1 Reproductive toxicity, STUDY 2, Table 6.6.1.2, Food consumption, Macroscopy	Notifier: Page 125 Table 6.6.1.2 (Vol.3): At food consumption, "ic"s for 300, 500, 1000 (mg/kg food) of male should be removed, and "dc" for 1000 (mg/kg food) of male should be added. The key to the pathology findings is confusing. We propose to add footnote "j" (j: observed in dead animals) to the three findings for females and amend "f" to show that male data are for animals killed after 12 weeks. There are differences between the values/marks in Table 6.6.1.2 and the data in the study report. Food consumption was decreased during the early part of the treatment period but increased during the later stages of the study. This is not adequately represented in Table 6.6.1.2. It would be better to include information on doses at which food consumption was	RMS: With regard to food consumption: disagree, see table 4 of the study report. Food consumption in males was only significantly decreased at day 3 in the 1000 mg/kg food group. The other data show consistently that compared to the control, food consumption in male rats was increased at 300, 500 and 1000 mg/kg food. With regard to the proposed footnote 'j': the macroscopy findings in females (liver enlarged, liver congestion and adrenal enlarged) were indeed observed in dead animals. The RMS, however, did not add this footnote in the DAR, because it does not change the conclusion and it does not change the relevance of the finding. With regard to footnote 'f': the fact that these data are for animals killed after	See open point in 2(16).

Reproductive toxicity (B.6.6)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		reduced in Table 6.6.1.2 as increased food consumption is not of toxicological importance. The macroscopic findings for females (liver enlarged, liver congestion and adrenal enlarged) are for dead animals only and the findings for males are for animals killed after 12 weeks.	12 weeks is 'normal' and it is therefore not necessary to describe this in a footnote.	
2(15)	Vol. 3, B.6.6.1 Reproductive toxicity, STUDY 2, Conclusions	Notifier: Page 127 2nd paragraph 3rd & 5th sentences (Vol.3): Notifier considers that salivation was toxicologically meaningless, because the finding was transient, and that the increased food consumption noted in males at 300 and 1000 mg/kg bw/day and in females at 1000 mg/kg bw/day was not toxicologically important for pyriproxyfen. Notifier proposes to add a sentence of "Salivation was transient and thought to be toxicologically meaningless" after the 3rd sentence and a sentence of ", however it was not toxicologically important" after the 5th sentence.	RMS: These findings were described because they were probably treatment-related. Whether these findings are adverse or not is difficult to assess; they are at least toxicologically not very important, and these findings did therefore not trigger the derivation of the NOAELs. The RMS proposes not to amend the text in the DAR.	Addressed.
2(16)	Vol. 1, Level 2, 2.3.1.2 Toxicodynamics, Reproduction and developmental toxicity Vol. 3, B.6.6.1	Notifier: Page 25 3rd paragraph (Vol.1), page 126 Table 6.6.1.2, page 127 3rd paragraph 1st sentence &5th paragraph 3rd sentence, page 139 Table 6.6.3.1, page 140 3rd paragraph 2nd-3rd sentences (Vol.3): Notifier considers that decreased numbers of corpora	RMS: Agree. Appendix III of the study report contains historical control data from 12 studies, performed during 1986-1987. The number of corpora lutea in the control, 100, 300, 500 and 1000 mg/kg food group is respectively 15.8 ± 1.30, 15.4 ± 1.50, 15.9 ± 1.18,	Open point 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.

Reproductive toxicity (B.6.6)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	Reproductive toxicity, STUDY 2, Table 6.6.1.2 and Conclusions Vol. 3, B.6.6.3 Summary and Table 6.6.3.1, Teratogenicity and reproductive toxicity study	lutea and live foetuses, and increased placenta weights were not treatment related in the combined teratology and reproductive toxicity study (Reproductive toxicity STUDY 2). The NOAEL for developmental toxicity should therefore be 1000 mg/kg bw/day, the highest dose tested. Corpora lutea and live fetuses: Notifier considers that the reduced numbers of corpora lutea and of live foetuses observed at 1000 mg/kg bw/day were not treatment related, because the differences were marginal and within the range of historical controls. This is noted in Appendix111 of the study report. Therefore, Notifier suggests that the words, "and decreased numbers of corpora lutea." in Vol.1&Vol.3 (Summary) and "(the number of) corpora lutea and" in Vol.3 (both Study 3, Summary table - Critical effects) should be deleted. Placental weights: An increase in placental weight was observed at 1000 mg/kg bw/day, but the effect was slight and no adverse effect was noted in foetuses. In the teratogenicity study in rats, no change was observed in placental weights even at 1000 mg/kg bw/day. Therefore, it was not considered to be	15.3 ± 1.42 and 14.2 ± 1.27. This historical control data show a mean no. of corpora lutea of 15.0 and a range of 13.7-16.0 (no standard deviations presented). The number of live fetuses in the control, 100, 300, 500 and 1000 mg/kg food group is respectively 14.3 ± 2.71, 12.6 ± 2.81, 14.4 ± 1.53, 13.1 ± 1.78 and 12.6 ± 1.67. This historical control data show a mean no. of live foetuses of 13.2 and a range of 11.9-14.4 (no standard deviations presented). The RMS agrees with the notifier that the words "and decreased numbers of corpora lutea." in Vol.1&Vol.3 (Summary) and "(the number of) corpora lutea and" in Vol.3 (both Study 3, Summary table - Critical effects) should be deleted. To be amended in a revised DAR and in an addendum, since the above presented figures will be presented in an addendum. An increase in placental weight was observed at 1000 mg/kg bw/day, but the effect was slight and no adverse effect was noted in foetuses. The RMS agrees with this conclusion and	

Reproductive toxicity (B.6.6)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		toxicologically significant, so that the concerning words, “and based on a decreased number of live foetuses and increased placenta weights.” in Vol.1&Vol.3 (Summary), and “but the number of corpora lutea and live foetuses were significantly lower and placental weights were significantly higher in dams at 1000 mg/kg bw/day.” in Vol.3, should be deleted.	considers this effect not adverse. In the teratogenicity study in rats, indeed no change was observed in placental weights, even at 1000 mg/kg bw/day (see B.6.6.2, STUDY 1). It should be noted, however, that the developmental NOAEL in that teratogenicity study in rats is lower, 100 mg/kg bw/day. In conclusion, the RMS agrees with the notifier and proposes a developmental NOAEL of 1000 mg/kg bw/day.	
2(17)	Vol. 3, B.6.6.2 Teratogenicity studies, STUDY 1, Characteristics	Notifier: Page 128 Characteristics (Vol.3): “Teratogenic effects: ≥ 1000 mg/kg bw/day” should be changed to “Teratogenic effects: Not teratogenic”, because no teratogenicity was observed even at the highest dose level.	RMS: see 2(13).	Addressed.

Reproductive toxicity (B.6.6)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(18)	Vol. 3, B.6.6.2 Teratogenicity studies, STUDY 1, Table 6.6.2.1, Post implantation loss	Notifier: Page 130, Table 6.6.2.1 Post implantation loss (Vol.3): Early post implantation losses in the groups given 0 and 100 mg/kg bw/day should be 4.4 and 6.7 respectively and not 4.0 and 7.0 respectively. The early post implantation rate was not statistically different and Notifier considers that values should be changed to "No treatment-related findings".	RMS: The number of early post implantation losses in the groups given 0 and 100 mg/kg bw/day should indeed be 4.4 and 6.7, respectively. To be amended in a revised DAR. The RMS does however not agree with the notifier to consider the finding in early post implantation losses as not treatment-related, just because it is not statistically significant.	Open point 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 discussion. See also 2(25).
2(19)	Vol. 3, B.6.6.2 Teratogenicity studies, STUDY 1, Conclusions	Notifier: Page 131, the last paragraph 2nd sentence (Vol.3): In the rat teratogenicity study, the litter size and the early post implantation rate were not statistically different and Notifier considers that the sentences should be removed.	RMS: The RMS proposes not to remove the sentence, but to delete the words 'statistically significant', because the increase of early implantation loss was indeed not statistically significant. To be amended in a revised DAR. See also 2(18).	Addressed RMS to consider in a revised DAR of corrigendum.
2(20)	Vol. 3, B.6.6.2 Teratogenicity studies, STUDY 2, Characteristics	Notifier: Page 132 Characteristics (Vol.3): "Teratogenic effects: 300 mg/kg bw/day" should be changed to "Teratogenic effects: Not teratogenic", because no teratogenicity was observed even at the highest dose level.	RMS: see 2(13).	Addressed

Reproductive toxicity (B.6.6)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(21)	Vol. 3, B.6.6.2 Teratogenicity studies, STUDY 2, Table 6.6.2.2	Notifier: Page 133 (Vol. 3): The number of Non-pregnant females and Excluded females appear twice in the table, the second set of data could be deleted.	RMS: Disagree. These figures are not the same. The number of copulated females minus the non-pregnant females and minus the excluded females results in the no. of dams examined.	Addressed RMS to consider in a revised DAR or corrigendum (with a revised table 6.6.2.2 with a single line for the Non pregnant females and a single line for the Excluded females)
2(22)	Vol. 3, B.6.6.3 Summary and Table 6.6.3.1	Notifier: Page 139 Table 6.6.3.1, page 140 2nd paragraph (Vol.3): Notifier considers that no effect on developmental toxicity was observed even at 1000 mg/kg bw/day in the rat teratogenicity and reproductive toxicity study and the NOAEL was 1000 mg/kg bw/day (See the comment point No. 2(16) and requests the RMS to reconsider the evaluation of this study in the DAR.	RMS: Agree. See response at 2(16). To be amended in a revised DAR.	Addressed See open point in 2(16)
2(23)	Vol. 3, B.6.6.2 Teratogenicity studies, STUDY 3, Conclusions Vol. 3, B.6.6.3 Summary and Table 6.6.3.1, Peri-post natal study	Notifier: Page 138 5th paragraph, 1st sentence, page 139 Table 6.6.3.1, Peri-post natal study & page 141 1st paragraph, page 152 1st paragraph (Vol.3): Notifier considers that the findings (increased incidences of renal pelvis dilatation and hyperaemia and/or inflammatory cell infiltration in the propria of the urinary bladder)	RMS: Disagree. Although these effects were not observed at 8 weeks postpartum, they were observed at 3 weeks postpartum, and can be relevant. These findings were not observed in the rat teratogenicity study, but results of two different studies can vary and this does not necessarily mean that the findings are	Open point 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.

Reproductive toxicity (B.6.6)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		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.	not relevant.	
2(24)	Vol. 3, B.6.6.3 Summary and Table 6.6.3.1	Notifier: Page 139 Table 6.6.3.1, page 140 1st, 2nd, 3rd and 4th paragraphs (Vol.3): The NOAELs for reproduction and for teratogenicity in the 2-generation study, the teratogenicity and reproductive toxicity study and the rat teratogenicity studies should be >the values quoted and not ≥ the values quoted to be consistent with the summaries on the following pages.	RMS: Disagree. It is correct that no teratogenic and reproductive effects were observed in the studies. Therefore the NOAELs are indicated as ≥. The NOAELs are not necessarily > than the values presented. Using the ≥ sign in this case is common practice. With regard to the NOAEL for teratogenicity in the rabbit study: The	Open point Experts to confirm the NOAELs in the rabbit teratogenicity study (maternal and developmental).

Reproductive toxicity (B.6.6)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		Also, 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.	number of dams remaining in the top dose group was insufficient for useful evaluations and the NOAEL for developmental and teratogenic effects was therefore established at 300 mg/kg bw/day and not at 1000 mg/kg bw/day, see DAR Vol. 3, page 135.	
2(25)	B.6.6.2, Teratogenicity studies, p.128 Vol.1, p.103, LoEP	EFSA: The statistically increased and dose-related incidence of skeletal variation (opening of the foramen transversarium of the 7th cervical vertebra) to be discussed in relation with the determination of the developmental NOAEL. The list of end points should be amended with the lowest developmental NOAEL related to this effect.	RMS: This effect was taken into account and the developmental NOAEL is therefore 100 mg/kg bw/day.The value in the list of endpoints, however, (≥ 1000 mg/kg bw/day) is not correct. The RMS will amend the list of endpoints (the format of the LOEP will be amended to the new format anyway).	Addressed See open point in 2(18)

Summary of mammalian toxicology and setting of ADI, AOEL and ARfD (B.6.10)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(26)	Vol. 1, Level 2, 2.3.3 ARfD (acute reference dose) Vol. 1, Level 2, Appendix 3,	Notifier: Pages 27-29, page 103, page 142 (Vol.1) and pages 153–155 (Vol.3): Since the only alert for the establishment of the ARfD is the	RMS: The RMS acknowledges that the 'Guidance for setting an ARfD' was very strictly interpreted. The RMS decided to present the 'worst-case	See open point in 2(27)

Summary of mammalian toxicology and setting of ADI, AOEL and ARfD (B.6.10)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	ARfD (acute reference dose) Vol. 1, Level 3, 3.1 Background to the proposed decision Vol. 3, B.6.10.4 ARfD (acute reference dose)	observed mortality and clinical signs in the acute oral toxicity study in mice and there are no further alerts, Notifier believes that it is not necessary to set an ARfD taking into account the EU document 'Guidance for setting an acute reference dose' (7199/VI/99 rev 5) and the daily consumption of residues. The RMS also proposes to discuss this further in the expert meeting. The EU document '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 LD_{50} testing) (Chapter 4.4). However, this does not mean that an ARfD must be set if there are adverse clinical signs 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, notifier does not consider this is a correct interpretation of the guidance. The above guidance only means that an ARfD is not needed if there are no adverse clinical signs or deaths at 2000 mg/kg, the limit dose recommended by the EU testing guidelines. There is no strict requirement to set an ARfD when deaths or clinical signs occur at the limit dose.	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.	

Summary of mammalian toxicology and setting of ADI, AOEL and ARfD (B.6.10)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		The only alert is observed in male mice at 2000 mg/kg of the limit dose and there are no further alerts. On the basis of low acute toxicity data of pyriproxyfen, Notifier considers that it is not necessary to allocate an ARfD. 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 0.07% by Dutch and UK models and 0% by FAO/WHO models for both adults and children (See details in Volume 3, Annex B, B.7.15.3 and B.7.15.4). The EU guidance states that under the above circumstances an ARfD is not necessary. The JMPR (FAO/WHO, 2004) also states that the numerical cut-off for setting ARfDs was about 5 mg/kg bw; i.e. if calculations indicated that an ARfD would be greater than this value (RMS proposes an ARfD of 10 mg/kg bw), then it would not be necessary on practical grounds to set an ARfD. As acute effects only occur at high		

Summary of mammalian toxicology and setting of ADI, AOEL and ARfD (B.6.10)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		doses that are considerably greater than the daily consumption of residues, an ARfD is not needed to ensure safe use of pyriproxyfen. In addition, based on the same toxicological data, The JMPR (FAO/WHO, 1999) concluded that it was not necessary to establish an ARfD. Notifier believes without a doubt that it is not necessary to set up an ARfD.		
2(27)	Vol. 3, Chapter B.6.10.4 (ARfD)	DE: Proposal: We propose to use the developmental study in rats (Saegusa 1988c) instead of the acute oral toxicity studies to derive the ARfD. 12/42 dams out of the high dose group died between day 4 and day 9 of dosing. Bodyweight decrease was observed in this group following the first dosage. Incidence of skeletal variation were increased in high and mid dose group pups. Using the developmental NOAEL of this study (100 mg/kg bw/d) and a safety factor of 100 results in the ARfD of 1 mg/kg bw/d.	RMS: It is difficult to assess whether the mortality of the dams and the skeletal variation in the pups can be the result of one single dose. The body weight decrease is obviously an acute effect, but it should be discussed if this is a relevant basis for the ARfD. See also 2(26).	Open point Setting of the ARfD to be discussed by the experts See also 2(26).
2(28)	Vol. 1, Level 2, 2.3.4	Notifier: Page 29, page 103 (Vol.1),	RMS: Because there seems to be no	Open point

Summary of mammalian toxicology and setting of ADI, AOEL and ARfD (B.6.10)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	AOEL Vol. 1, Level 2, Appendix 3, AOEL Vol. 1, Level 3, 3.1 Background to the proposed decision Vol. 3, B.6.10.5 AOEL	pages 155-156 (Vol.3): Notifier suggests that 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, even if chronic exposure occurs by the re-entry activities. 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 to select the NOEL of 10 mg/kg	effect of exposure duration, 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. Derivation of the AOEL to be discussed at the PRAPeR meeting.	Derivation of the AOEL to be discussed by the experts (relevant species, relevant study, correction for oral absorption) See also 2(29).

Rapporteur:

Summary of mammalian toxicology and setting of ADI, AOEL and ARfD (B.6.10)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		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. (See details in Volume 3, Annex B, B.6.3.4 Semichronic oral studies, STUDY 4, and the comment No.2(4). Therefore, it can be assumed that the real NOAEL in this study is just slightly lower than 30 mg/kg bw/day. As for NOAEL of 13.3 mg/kg bw/day, which the RMS considers the next lower NOAEL, Notifier considers that the dose of 76.4 mg/kg bw/day should be selected as the NOAEL for 2-generation study in rats (See the comment No. 2(12). Therefore, the overall NOAEL of 23.5		

Summary of mammalian toxicology and setting of ADI, AOEL and ARfD (B.6.10)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		mg/kg bw/day in the 13-weeks oral toxicity study in rats is the most appropriate selection for the derivation of the AOEL.		
2(29)	Vol. 1, Level 2, 2.3.4 AOEL Vol. 1, Level 3, 3.1 Background to the proposed decision Vol. 3, B.6.10.5 AOEL	Notifier: Page 29, page 142 (Vol.1) and page 155 (Vol.3): Notifier suggests that a systemic AOEL of 0.148 mg/kg bw/day should be set. Notifier considers that the absorption of 63% propsed in the dossier is already a worst case estinate and that the AOEL should be based on the NOAEL from the short-term toxicity study, 23.5 mg/kg bw/day. See the comments in both No. 2(1) and No. 2(28). Therefore, A systemic AOEL of 0.148 mg/kg bw/day should be set.	RMS: The RMS considers an oral absorption of 40% the most appropriate value, see 2(1). With regard to the derivation of the AOEL, see 2(28).	See open point in 2(28).
2(30)	Vol. 1, Chapter 2.3 (List of endpoints)	DE: Remark: There is a typing error for the AOEL value (0.1 instead of 0.04 mg/kg bw/d). Comparing following values with the summary in Table 6.6.3.1, reproductive NOAEL should probably read 333 instead of 443 mg/kg bw/d and the developmental NOAEL should probably read 100 instead of 1000 mg/kg bw/d.	RMS: Agree, the values in the list of endpoints will be amended.	Open point RMS to revise the list of end points also taking into consideration the discussion at the meeting of experts.

Dermal absorption (B.6.12)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(31)	B.6.12, Dermal absorption, p.163	EFSA: It should be clarified that the two doses are representative for the undiluted product and the spray dilution (to the minimum recommended use concentration for field application).	RMS: The EC formulation tested contains pyriproxyfen at the same concentration as in the commercial EC concentrate (100 g/L). This formulation is applied as such to the skin (10 µl/cm^2), resulting for the concentrate (per definition) in a representative area dose of about 1 mg/cm^2. The area dose of the spray dilution (0.17 µg/cm^2) represents the lowest dose rate of 0.02 kg a.s./ha and this is thus the lowest, and therefore worst-case, possible area dose.	Open point Dermal absorption values to be confirmed by the experts.

Exposure data (B.6.14)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(32)	Vol. 3, B.6.14.2.1, Internal exposure and risk assessment	UK: In Tables 6.14.2.1 – 6.14.2.3, only route specific exposure values (dermal and respiratory) have been compared individually to the systemic AOEL. It is more appropriate to base the 'risk-index' on a comparison of total systemic exposure values with the AOEL.	RMS: Agree. Nowadays we present exposure values differently and we also do not use the 'risk-index' anymore, but %AOEL. In case the AOEL changes after discussion at PRAPeR, the exposure assessment can be recalculated and presented in an addendum according to current practice.	Open point RMS to provide revised exposure calculations (with final results in % of AOEL) after agreement of the AOEL.
2(33)	Vol. 3, B.6.14.2.1, Internal exposure and risk assessment	UK: In Tables 6.14.2.2 and 6.14.2.3, a body weight assumption of 70 kg has been used in the risk assessment for bystanders and harvest workers. As these groups are likely to include females and young people, a body weight assumption of 60 kg may be more appropriate.	RMS: There are no harmonised EU defaults for bystander and worker weight. The RMS considers 70 kg more appropriate.	Open point Bystander exposure to be confirmed by the experts (with regard to the parameters used in the calculations).
2(34)	Vol. 3, Appendix 3, Section 2.4 Dutch Glasshouse Model	UK: No details have been provided for the Dutch Model calculations other than the usage information and the calculated exposure values. For transparency, further details of the calculation should be provided.	RMS: Agree. In the meantime, a new spreadsheet in English has been developed for the Dutch greenhouse model. The model calculations will be presented in the new detailed spreadsheet in an addendum.	Open point Detailed calculations of operator exposure with the Dutch greenhouse model to be provided in an addendum. See also 2(35).
2(35)	Vol. 3, B.6.14.3, Conclusions	UK: Although the Dutch Model estimates indicate that the Southern European use of 'Pyriproxyfen 10EC' on glasshouse crops will result in a level	RMS: This is not exactly what was described in the DAR. The point is that for indoor uses in Southern Europe, the exposure was 109% of	See open point in 2(34).

Exposure data (B.6.14)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		of operator exposure without the use of PPE which exceeds the AOEL, the DAR concludes that this use is acceptable in view of the worst case assumptions made in the model. It would be useful for this conclusion to be supported with alternative estimates using EUROPOEM data for glasshouse applications.	the AOEL without the use of PPE (risk-index of 0.04 and of 1.05 for respiratory and dermal exposure, respectively). It was argued in the DAR that considering the worst-case assumptions made with establishment of the AOEL and exposure calculations, this exceeding is considered negligible. In case this conclusion is not acceptable, there is still a safe indoor use in Southern Europe with PPE. With regard to exposure estimates with EUROPOEM: The database for this scenario in EUROPOEM is very small, resulting in the fact that not a 75th percentile, but the highest value measured will be taken into account. This results in such a high exposure estimate, that the calculations based on the larger Dutch greenhouse model database are considered more appropriate.	

Exposure data (B.6.14)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(36)	Vol. 3, Appendix 3, Section 4 Worker Exposure	UK: As 'Pyriproxyfen 10EC' is applied up to 2 times on glasshouse crops, the exposure estimates (currently based on a single application/crop) should consider the likelihood of a build up of foliar residues from repeated applications.	RMS: The supported use involves 1-2 applications with a 10-d spray interval. This implicitely means that after 10 days, the mean surface dose is decreased to a non-efficasious level. Although build up of foliar residues can occur to some extent, it cannot be quantified. There is no methodology available for a re-entry exposure assessment after repeated applications.	See open point in 2(37).
2(37)	Vol. 3, Appendix 3, Section 4 Worker Exposure	UK: No details have been provided for the Dutch Model calculations for re-entry exposure in glasshouses other than the usage information and the calculated exposure values. For transparency, further details of the calculation should be provided.	RMS: Agree. Re-consideration of the available models however, resulted in the current view that EUROPOEM II is a more suitable model to estimate re-entry exposure in glasshouses. Re-calculation of re-entry exposure with EUROPOEM II results in comparable results: exposure of 11% of the AOEL for indoor use for Northern Europe (instead of 13% in the DAR) and exposure of 41% of the AOEL for indoor use for Southern Europe (instead of 50% in the DAR). The calculations with EUROPOEM II will be presented in detail in an addendum.	Open point 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. See also 2(36), 2(28)

Exposure data (B.6.14)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(38)	Vol. 3, Appendix 3, Section 4 Worker Exposure	UK: As harvest workers may not be aware of which products have been applied to the crop in which they are working or of the precautions to be taken as a result, it may not be appropriate to assume that these workers will wear PPE other than that used habitually when carrying out harvesting operations.	RMS: Preferably workers should not be required to wear PPE in general (from an occupational hygiene perspective). However, for pyriproxyfen all uses have been calculated to be safe for workers without PPE anyway.	See open point in 2(37).

Other comments				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(39)	Vol.3, B.6, General comment	EFSA: Tables with figures instead of statements (increased, decreased, …) would be more helpful for the interpretation of the results.	RMS: Presentation of the results is a matter of preference. The RMS presents the results in tables indicating decreased or increased, because this makes it possible to consider the complete toxicological picture of a study and really observe/evaluate relevant combination(s) of effects instead of focussing on individual effects. All relevant values were subsequently described in the text.	Addressed. (further details have been required for the relevant studies to be discussed)
2(40)	Vol.4, C.1.4.1, p.17	EFSA : RMS to confirm that the levels of the impurities in the final technical	RMS: The chemical purity of pyriproxyfen technical is relatively high: 97%. All tox	Open point Experts to discuss whether the level of

Other comments				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		specification are acceptable in comparison to what has been tested in the toxicological batches.	studies have been performed with two batches: PTG-86011 and PYG-87074 (except for the 21-d dermal study which was performed with batch 007024). With batch PYG-87074, the following studies were performed: 13-w rat, two 1-y dog, *in vitro* HGPRT, *in vitro* UDS, *in vivo* micronucleus, 2-y rat, 78-w mouse and 2-generation reproduction. All other studies were performed with batch PTG-86011. Both batches are highly comparable to the technical specification. The critical studies for derivation of the endpoints used batch PYG-87074. This batch contains equal or slightly higher levels of the impurities in the specification. This material tested in the tox studies is therefore considered to be equivalent to the technical specification. Except for impurity 1, batch PTG-86011 is also equivalent to the technical specification.	toluene (relevant impurity) in the **final** technical specification is covered by its level in the toxicological batches.

Other comments				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
2(41)	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 pyrifproxyfen.'* should be confirmed by the meeting of toxicology. See also 3(2)			Open point 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.
2(42)	Comment related to 1(6) and concerning the isomers of pyriproxyfen (raised by EFSA after the written procedure)			Open point 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.

Comments received on reporting table, section Mammalian Toxicology (B.6)			
Reference to reporting table	MS / Notifier	Comment	EFSA response
2(1)	NL	Disagree with this open point. All relevant details are already presented in the DAR. The point is that based on the results, the notifier draws a different conclusion with regard to the oral absorption rate than the RMS did in the DAR. NL proposes to discuss the oral absorption rate in	Noted.

Rapporteur:

Comments received on reporting table, section Mammalian Toxicology (B.6)			
Reference to reporting table	MS / Notifier	Comment	EFSA response
		the expert meeting.	
2(3)	NOT	The historical control data will be provided. Proposed submission date: 01 December 2007	Noted.
2(10)	NL	There are no additional figures to present. In Table 6.6.1.1 no figures were presented for the liver effects, but the figures are on the next page in the DAR, described in the text. The problem is that histopathology was not performed on the livers of all animals of the 200 and 1000 mg/kg food groups and that makes the effects on liver weight difficult to interpret (adverse or not). NL proposes to discuss this point in the expert meeting.	Noted.
2(28)	NOT	Notifier considers that the absorption of 63% proposed in the dossier is already a worst case estimated and that the AOEL should be based on the NOAEL from the short-term toxicity study, 23.5 mg/kg bw/day. Therefore, a systemic AOEL of 0.148 mg/kg bw/day should be set.	Noted.
2(41)	NOT	PYPA can be formed from either pyriproxyfen, 4'-OH-pyr (a major metabolite) or DPH-pyr via cleavage of the ether linkage between the aromatic ring and the alkyl group-and subsequently oxidized to PYPAC ((*RS*)-2-(2-pyridyloxy)-propionic acid). PYPA was not detected in urine or feces in the rat metabolism study (Yoshino, 1993a). However, PYPAC was identified and quantified in urine, accounting for 1.0 to 4.9% of the applied dose (an urinary major metabolite). The existence of PYPAC demonstrated that either pyriproxyfen, 4'-OH-pyr (a major metabolite) or DPH-pyr was transformed to PYPA via the above route and then oxidized to PYPAC in rats. As PYPA has been formed as a result of the metabolism of pyriproxyfen, rats have been exposed to PYPA during the toxicological studies conducted with pyriproxyfen. The results of the studies of pyriproxyfen therefore already take into account any effects due to PYPA. Even if PYPA had not been a metabolite in rats it would be predicted to be of low toxicity; the structure of this metabolite is not associated with any toxicological alerts and it is oxidised to a polar metabolite, PYPAC, which is rapidly excreted. The findings of rat *in vivo* metabolism demonstrated that PYPA was formed as an intermediate to PYPAC when pyriproxyfen is administered. Therefore, PYPA is toxicologically non-relevant.	Noted.

3. Residues

Metabolism in plants (B.7.1)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(1)	Vol. 3, B.7.1.1 Primary crops, STUDY 2	Notifier: Page 184 4th paragraph (Vol.3): A typographical error of "2'-OH-PYR" should be changed to "2-OH-PY".	RMS: Agrees. See also 3(11) To be ammended in revised DAR	Addressed May be considered in a revised DAR/ corrigendum as appropriate
3(2)	Vol. 3, B.7.1.1, Tomato metabolism	EFSA: The conclusion that residues of the free and conjugated PYPA metabolite would not be relevant in tomatoes harvested at PHI 3 because the PHI in the metabolism study (7 days) in longer than the one defined in the GAP (3 days) lacks the consideration that a) PHI 3 days is a minimum waiting period, not obliging the farmer to harvest after exactly 3 days and no later, and b) the metabolic activities in the fruits continue after harvest.	RMS: Agrees: for risk assessments also longer PHI should be taken into account. PYPA and conjugated PYPA account for 0.025 mg/kg (9.4% TRR) in the fruit juice juice in the metabolism study performed with 3x148 g ai/ha (2x overdose). Pyriproxyfen (mainly present in the pomace) accounts for 0.13 mg/kg (48% TRR). At the expected dose rate of 224 g ai/ha, PYPA and conjugated PYPA will be lower (might be half of the amount found in the metabolism study). The metabolite was not found in rat, but should be th only logic product of hydrolysis of the ether bond of pyriproxyfen. It's toxicology is taken into account in the toxicological profile of pyrifproxyfen. Since it's level might be around 0.01 mg/kg and it is only 20% of parent pyriproxyfen, no conversion factor for risk assessment is proposed. Addressed	Open point The RMS asessment*: '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 pyrifproxyfen.'* 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.

Rapporteur:

Metabolism in livestock (B.7.2)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(3)	Vol. 3, B.7.2.1 Ruminants, STUDY 1 and STUDY 2	Notifier: Page 204 4th paragraph 1st sentence (Vol.3) and page 216 2nd paragraph 1st sentence (Vol.3): A typographical error of "eggs" should be changed to "milk".	RMS: Agrees, 'eggs' should be 'milk' To be ammended in revised DAR	Addressed May be considered in a revised DAR/ corrigendum as appropriate
3(4)	Vol. 3, B.7.2.1 Ruminants, STUDY 1 and STUDY 2	Notifier: Page 204 4th paragraph 2nd sentence (Vol.3) and page 216 2nd paragraph 2nd sentence (Vol.3): A typographical error of "hen samples" should be changed to "goat samples".	RMS: Agrees, 'hen' should be 'goat' To be ammended in revised DAR	Addressed May be considered in a revised DAR/ corrigendum as appropriate
3(5)	Vol. 3, B.7.2.1 Ruminants, STUDY 1 and STUDY 2 Poultry, STUDY 1 and STUDY 2	Notifier: Pages 207-212 Table B.7.2.1-2 to -9 (Vol.3), pages 220-223 Table B.7.2.1-13 to -19 (Vol.3), pages 231-232 Table B.7.2.1-23 to -25 (Vol.3) and pages 239-240 Table B.7.2.1-30 to -31 (Vol.3): Total of 35 typographical errors of "sulphate" should be changed to "sulfate".	RMS: Agrees, nowadays we write sulfate. To be ammended in revised DAR	Addressed May be considered in a revised DAR/ corrigendum as appropriate
3(6)	Vol. 3, B.7.2.1 Ruminants, STUDY 1	Notifier: Page 209 Table B.7.2.1-4 (Vol.3): A typographical error of "14C" should be changed to "^{14}C".	RMS: Agrees. To be ammended in revised DAR	Addressed May be considered in a revised DAR/ corrigendum as appropriate
3(7)	Vol. 3, B.7.2.1 Ruminants, STUDY 2	Notifier: Page 215 3rd paragraph 1st and 2nd sentence (Vol.3): Two typographical errors of "study 3" should be changed to "study 1".	RMS: Agrees. To be ammended in revised DAR	Addressed May be considered in a revised DAR/ corrigendum as appropriate
3(8)	Vol. 3, B.7.2.1 Ruminants, STUDY 2	Notifier: Page 223 Table B.7.2.1-19 (Vol.3): A typographical error of "Identification()"should be changed to "Identification$^{(A)}$".	RMS: Agrees. To be ammended in revised DAR	Addressed May be considered in a revised DAR/ corrigendum as appropriate

Rapporteur:

Metabolism in livestock (B.7.2)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(9)	Vol. 3, B.7.2.2 Poultry, STUDY 1	Notifier: Page 228 3rd paragraph 1st sentence (Vol.3): A typographical error of "and thigh" should be deleted because the same descriptions repeated in the next paragraph.	RMS: Agrees. To be ammended in revised DAR	Addressed May be considered in a revised DAR/ corrigendum as appropriate
3(10)	Vol. 3, B.7.2.2 Poultry, STUDY 1	Notifier: Page 233 3rd paragraph 1st sentence (Vol.3): A typographical error of "0.004-0.0049 mg eq /kg" should be changed to "0.004-0.049 mg eq /kg".	RMS: Agrees. To be ammended in revised DAR	Addressed May be considered in a revised DAR/ corrigendum as appropriate
3(11)	Vol. 3, B.7.2.1 Poultry, STUDY 2	Notifier: Pages 235-242 (Vol.3): Total 8 typographical errors of "2-OH-pyridine" and 2-OH-pyridine should be changed to "2-OH-PY".	RMS: Agrees, furthermore, in the tables, 2-OH-PYR should be 2-OH-PY. See also 3(1) To be ammended in revised DAR	Addressed May be considered in a revised DAR/ corrigendum as appropriate
3(12)	Vol. 3, B.7.2.4 List of identified compounds	Notifier: Page 244-245 Table (Vol.3): Crop/Commodity of PYPA, "Hen (skin with fat)", should be changed to " Hen (gizzard)".	RMS: PYPA is present in ,hen, skin with fat' as well as 'hen gizzard' To be ammended in revised DAR	Addressed May be considered in a revised DAR/ corrigendum as appropriate
3(13)	Vol. 3, B.7.2.2 Poultry, STUDY 2	Notifier: Page 241 Table B.7.2.1-33 (Vol.3): Symbols of (C) should be added to Extractable of Day 3 excreta of both values, 92 and 7.2, and symbols of (D) should be added to Extractable of Day 7 excreta of both values, 94 and 7.4, respectively.	RMS: Agrees. To be ammended in revised DAR	Addressed May be considered in a revised DAR/ corrigendum as appropriate

Residue definition (B.7.3)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(14)	Vol 3, B.7.3.1, definition of residue in plants	UK: We agree with the residues definition in plants as parent pyriproxyfen only, as this is the major component in plants, with none of the metabolites being present at significant amounts in the plants at harvest.	RMS: Agrees. Addressed.	refer to open point in 3(2)
3(15)	Vol 3, B.7.3.2, definition of residue in animal products	UK: we agreed that a residue definition in animal products is not required as the crops are not usually fed to animals.	RMS: Agrees. Addressed.	Addressed

Processing (B.7.7)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(16)	Vol.3 B.7.7.2 Effects on residue levels	Notifier: Page 264 Guidelines and limitations point 2 (Vol.3): Pyriproxyfen residues in cotton seed are expected to be <0.01 mg/kg and not <0.1 mg/kg.	RMS: What is meant by the RMS: the trigger value of 0.1 mg/kg for performing processing studies is not exceeded. Indeed, pyripoxyfen is not only <0.1 but also <0.01 mg/kg To be clarified in revised DAR See also 3(17)	Addressed
3(17)	Vol.3 B.7.7.3 Summary of processing studies	Notifier: Page 264 1st paragraph 2nd sentence (Vol.3): Pyriproxyfen residues in cotton seed are expected to be <0.01 mg/kg and not <0.1 mg/kg.	RMS: See 3(16).	Addressed

Rapporteur:

Livestock feeding (B.7.8)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(18)	B.7.15.1. Intakes by domestic animals and B.7.3.2 Definition of the residue in animal products	EFSA: According to the current European Feed Composition Table only cotton seed would be a relevant commodity. However, cotton gin trash is known as a feed item relevant for cattle and relevant residue levels of pyriproxifen might be expected in gin trash (according to the metabolism study at 2N rate, which has been considered applicable to the proposed GAP by RMS) It should be mentioned that a scenario where gin trash is fed to cattle has not been evaluated.	RMS: Agrees. RMS is not very familiar with the feeding of Gin trash. Gin trash is not mentioned in the Lundehn docuemtn as feeding stuff. A very quick scan showed that gin trash might be fed to cattle up to 30% of the diet (dry weight). Since residues are found up to 1.53 mg/kg pyriproxyfen in the metabolism study with cotton perfrormed at 2N, intake might be up to 0.25 mg/kg dry feed in cattle. In the metabolism study with goat (5 daily doses with 10 mg/kg dry feed, 40N, TRR was up to 0.02 mg/kg (meat), 0.49 mg/kg (liver), 0.26 mg/kg (kidney) and 0.096 mg/kg (milk). Assuming that residue levels are more or less linear with feeding levels, at a feeding level of 0.25 mg/kg dry feed residues are expected to be 40-fold lower: ≤ 0.01 mg/kg TRR. To be ammended in revised DAR To be discussed in an expert meeting whether gin trash should be dealt with as a feed item	Open point 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 Open point RMS proposal: To be discussed in an expert meeting whether gin trash should be dealt with as a feed item

Rapporteur:

Succeeding/Rotational crops (B.7.9)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(19)	Vol. 3, B.7.1.2, Succeeding crops	EFSA: Some clarification should be given on the rotational crops issue. 4-OH-PYR is a relevant metabolite in soil compartment and also more persistent than parent as DT90 is up to 234 days. RMS could have elaborated on this. Only 30 days plant back interval was investigated, if metabolites are taken up, higher residues may occur at a later plant back interval. Apart from solvents partition, were any attempts made to identify the residues in wheat grain and straw? What does mean "when a correction is made for direct treatment … residue levels are not expected to exceed the trigger.	RMS: 'Correction for direct treatment' refers to the fact that the study was performed with 0.198 kg ai/ha on bare soil, without crop interception. Based on studies form Fate and Behaviour section, 4-OH-PYR is accumulating in soil, and metabolites from 4-OH-PYR might be accumulating in rotational crops at higher DAT. Uptake of these possible metabolites was not investigated since rotational crop studies were carried out with 30DAT only. However, since residues 30 DAT after application of a 1N dose without crop interception were low (< 0.01 mg/kg TRR in leafy and rooty crops, residues of 4-OH-PYR or it's degradation products were not expected.. In grain, TRR accounted for 0.081 mg/kg, from which 0.072 mg/kg was not readily extractable. A further 0.008 mg/kg was extractable in 1N HCl, 0.063 mg/kg in 6N HCl. Fraction after acid hydrolysis, however, were not further identified. ~~To be discussed in an expert meeting whether gin trash should be dealt with as a feed item~~	Open point 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 data.

MRLs related issues and Consumer Risk Assessment (B.7.10 to B.7.15)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(20)	Vol.3 B.7.12.3 Summary of proposed MRLs	Notifier: Page 267 Table (Vol.3): The STMR and HR for cotton seed should be "<0.01" mg/kg instead "0.01*". In addition, please add a footnote for "0.01*" in MRL column.	RMS: Can be argued about. However, for calculations the value of 0.01 mg/kg will be used anyway Addressed	Addressed
3(21)	Vol.3 B.7.15.2 Intakes by humans	Notifier: Page 270 Table B.7.15.2-2 (Vol.3): Consumption for cotton seed should read $0.00010^{(2)}$.	RMS: Agrees. To be ammended in revised DAR	Addressed May be considered in a revised DAR/ corrigendum as appropriate
3(22)	Vol 3, 7.12.1, proposed MRLs	UK: We agree with the proposed EU MRLs although we note that some other member states may ask for further cotton residue trials data	RMS: EFSA did. See 3(23). Addressed.	refer to 3(23)

Other comments				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
3(23)	Vol. 3, B.7.6.2, Cotton residue trials	EFSA: Given the fat solubility of parent and the results of the metabolism study (even though growth stage at application not indicated) it might be discussed whether 2 residue trials in cotton are indeed sufficient to exclude that occasionally residues >0.01 mg/kg in cotton seed may arise.	RMS: In view of the fact that the 2 trials were performed with a 30% overdose (1.3N), resulting in 2x < 001 mg/kg pyriproxyfen, and the metabolism study with cotton was performed with a 100% overdose (2N), resulting in 1.5 mg/kg and 0.00085 mg/kg pyriproxifen in the gin trash and the seeds, respectively, at 28DAT, residues are not likely to be transported to seeds to a large extent. Addressed.	Open point 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)
3(24)	Vol.3, B.7 Comment related to 1(6) and concerning the isomers of pyriproxyfen (raised by EFSA after the written procedure)	EFSA: Pyriproxifen is a racemic mixture of enantiomers, has this been considered in all areas of the risk assessment?		Open point 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

Comments received on reporting table, section Residues (B.7)			
Reference to reporting table	MS / Notifier	Comment	EFSA response
3(18) and 3(19)	NL	The RMS-proposal ‘to be discussed in an expert meeting whether gin trash should be dealt with as a feed item’ (column 3) is erroneously put under 3(19) instead of 3(18)	Corrected in the reporting table
3(19)	NOT	The confined rotational crop study of pyriproxyfen is conducted at the application rate of 80 g	Noted.

Rapporteur:

Comments received on reporting table, section Residues (B.7)			
Reference to reporting table	MS / Notifier	Comment	EFSA response
		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 from the application rate and method used for this study. Incidentally, the aerobic soil metabolism study shows that 4'-OH-Pyr is formed at the level of 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 most rationally exposed not only to pyriproxyfen but also to 4'-OH-Pyr at the rate of 0.108 ppm at least, assuming that 0.9 %AR of pyriproxyfen is transformed during the 30-day of plant back interval period. The concentration of 0.108 ppm corresponds to ten times greater value than the one calculated as the maximum plateau concentration, 0.013 ppm (SE), reached after one year application following 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. In the site, 4'-OH-Pyr was detected at the maximum of 0.02 mg/kg during Day 0 to 7 after the last application and the residue at Day 30 was just 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 clearly faster than the calculated DT50 of 24 to 70 days (mean 38 days) from the laboratory studies which is 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 if taking the degradation into consideration, the maximum formation of 4'-OH-Pyr in the field would be estimated as a 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 should be basically unlikely and insignificant even if it occurs.	
3(23)	NOT	The notifier agrees with the RMS that 2 residues trials should be sufficient to demonstrate a no residue situation based on the data generated to date.	Not relevant for the point at issue.

4. Environmental fate and behaviour

Route and rate of degradation in soil (B.8.1)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(1)	Vol. 1, Level 2, 2.5.2, Fate and behaviour in soil Vol. 3, B.8.1.3, Summary route and rate of degradation in soil	Notifier: In Table 2.5.2-1, on page 38, and in Table B.8.1.3-1, on page 320, the DT_{90} (20°C, d) of PYPAC should be 123, 70 and 1.3 days, mean 65 days, rather than 118, 69 and 1.3 days, mean 63 days, to be consistent with the DT_{90} values reported in Table B.8.1.1.1-18, on page 302. Please consider revising these values accordingly.	RMS: Correct, will be updated in revised DAR or addendum	Addressed RMS to consider in a corrigendum or revised DAR
4(2)	Vol. 1, Level 2, 2.5.2, Fate and behaviour in soil	Notifier: In Table 2.5.2-2, on page 40, the maximum soil DT_{50} for PYPAC used in the PEC_s calculations should be 37 rather than 36 days, to be consistent with the calculations reported in Vol. 3 of the DAR. Please consider revising this value accordingly.	RMS: True. This will probably not have any consequences for PEC_{twa} values and the risk assessment. Will be considered in a revised DAR.	Addressed RMS to consider in a corrigendum or revised DAR
4(3)	Vol 1 List of endpoints, Route of degradation in soil supplemental studies, soil photolysis	EFSA: LoEP Vol 1 p 111. Please add the DT50 calculated in the irradiated experiment including the equated natural light energy input (i.e. ca. 10-19 days summer sunlight at 43°N)	RMS: Will be added.	Addressed The LoEP has been updated (version dated July 2007).
4(4)	Vol. 1, Level 2, Appendix 3, List of endpoints	Notifier: On page 111, 'PYPAC DT_{50lab} (20°C, aerobic): 1.3 - 123 d' should read 'PYPAC DT_{90lab} (20°C, aerobic): 1.3 - 123 d'. Please consider revising this.	RMS: Correct. LoEP will be updated	Addressed The LoEP has been updated (version dated July 2007).

Rapporteur:

Route and rate of degradation in soil (B.8.1)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(5)	Vol. 1, Level 2, Appendix 3, List of endpoints	Notifier: On page 112, the DT_{50f} for the Washington soil should be 5.9 d, r^2 0.93, rather than 9.8 d, r^2 0.72 and the DT_{90f} should be 20 d, rather than 33 d, to be consistent with the information reported in the DAR. Please consider revising this in the list of endpoints.	RMS: Correct. LoEP will be updated	Addressed The LoEP has been updated (version dated July 2007).
4(6)	Vol 1 List of endpoints, Rate of degradation in soil, laboratory studies	EFSA: LoEP Vol 1 p 111. Please annotate the DT50 for 4-OH-Pyr to indicate that these values are rate of decline observed in a study dosed with the parent compound and are not true degradation rates for 4-OH-Pyr. For the 10°value for pyriproxyfen please add the range calculated (i.e. 6.2-55 days) and not just the mean value as currently presented.	RMS: We don't understand EFSA's saying about true degradation. DT_{50} values were fitted for the data from the maximum formation onwards where study data were appropriate. This is according to kinetic guidance. Agreed the range will be presented as well as the mean.	Open point 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.' Addressed in the LoEP version dated July 2007 regarding providing the range of values.

Adsorption,desroptionand mobility in soil (B.8.2)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(7)	Vol. 3, B.8.2.3, Summary of adsorption	EFSA: On page 335 of Volume 3 it is stated that no pH dependency of	RMS: The information on the relationship with pKa was meant to be for the parent only.	Point of clarification for the applicant. Applicant to provide pKa estimates (QSAR

Adsorption,desroptionand mobility in soil (B.8.2)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	desorption and mobility in soil Vol 1 List of endpoints, soil adsorption/desorption pH dependence.	adsorption at environmental relevant pH range is expected based on RMS estimated pKa values. A calculated pKa value is available for pyriproxyfen (phys chem. list of endpoints, 6.87) but not for the metabolites. Please provide the pKa values estimated and the estimation method used (Software version number etc.) for the two metabolites. As the metabolites are a phenol and a carboxylic acid, pH dependant adsorption might be expected. For pyriproxifen in acidic soils (not investigated) stronger adsorption might be expected. EFSA cannot accept the current statement regarding lack of pH dependant adsorption based on the information currently presented in the DAR. LoEP Vol 1 p 112. The statement No pH dependency is expected may need to be reconsidered.	For the metabolites there is some indication there might be some pH dependency, although there are just 3 data points considered to be reliable. However when we just consider the Kf values instead of Koc , these do not show any relation. Even when the 4th soil with very low o.c. is included in the consideration. To our opinion it is not possible to conclude on a single relation with 1 soil parameter based on such small dataset.	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.
4(8)	Vol 1 List of endpoints, soil adsorption / desorption	EFSA: LoEP Vol 1 p 112. Please add the units for Kf and Kfoc (presumably L/kg)	RMS: Correct, will be added,	Addressed The LoEP has been updated (version dated July 2007).

Rapporteur:

PEC in soil (B.8.3)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(9)	Vol. 3, B.8.3, Predicted environmental concentrations in soil. Vol 1 List of endpoints, PECsoil and Soil accumulation and plateau concetration	EFSA: On pages 338-339 of Volume 3 accumulated concentrations are presented for Northern and Southern Europe for the use on tomato / eggplant for metabolite 4-OH Pyr. As the SFO DT90 for this metabolite is 235 days (i.e. less than 365 days), when it is assumed one crop is grown per year accumulation would not be expected. Accumulated concentrations are however calculated, so presumably it was assumed more than 1 crop would be planted per year which would probably be the case for glasshouse production? However it is currently not stated that it was assumed several crops were grown per year. In fact it is stated yearly applications were assumed in calculations, though the application rate used as the yearly application is not stated? Clarification is needed regarding the calculations? LoEP Vol 1 p 112. The calculation for cotton can be deleted (there is no accumulation the level is the same as for a single application). For tomato / egg plant the endpoints need	RMS: True as the longest DT90 is<365 days it is not required to calculated PECacc. For tomatoes and eggplants in glasshouses in NE only one crop per year is grown. The provided calculations are superfluous. IN SE two crop per year are possible. The values for SE will be re-calculated with regard to this in an addendum. RMS: Agreed, but as there is no calculation in the first place we don't know what should be deleted. For tomatoes in SE PEC_{acc} should be recalculated and addressed in the LoEP.	Open point 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 updated as appropriate with these clarified accumulated 4-OH Pyr soil PEC. Open point 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. Addressed (Regarding the Cotton PEC and crop interception) as the LoEP has been updated (version dated July 2007).

PEC in soil (B.8.3)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		changing in line with the comment above on Vol. 3. LoEP Vol 1 p 113-116. For the cotton PEC (pyriproxifen and metabolites) calculations are presented assuming 40% crop interception. In the DAR 75% crop interception is appropriately assumed base on the growth stages in the intended uses table. The endpoints should be consistent with the calculation presented in the DAR.	RMS: Correct. LoEP will be updated	
4(10)	Vol. 1, Level 2, Appendix 3, List of endpoints	Notifier: On pages 113, 114-115 and 115-116, the crop interception factor for cotton used in the PEC_s calculations for pyriproxyfen and its metabolites 4'-OH-Pyr and PYPAC, should be 75%, rather than 40%, to be consistent with the calculations reported in the DAR. Please consider revising this and updating the PEC_s values in the list of endpoints accordingly.	RMS: Correct. LoEP will be updated	Addressed The LoEP has been updated (version dated July 2007).
4(11)	Vol. 1, Level 2, Appendix 3, List of endpoints	Notifier: On page 115, the DT_{50} for PYPAC used in the PEC_s calculations should be 37 rather than 36 days, to be consistent with the calculations reported in the DAR. Please consider revising this.	RMS: True. This will probably not have any consequences for PEC_{twa} values and the risk assessment.	Addressed

Rapporteur:

Fate and behaviour in water and impact on water treatment procedures (B.8.4-B.8.5)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(12)	Vol 1 List of endpoints, Route and rate of degradation in water, photolytic degradation	EFSA: LoEP Vol 1 p 116. Please quote the DT50 with its associated equivalent light intensity (xenon light isn't very helpful in putting the DT value in context). I.e. 8.5-14.5 days at 43°N summer sunlight is more useful.	RMS: Agreed, LoEP will be changed accordingly	Addressed The LoEP has been updated (version dated July 2007).
4(13)	Vol 1 List of endpoints, Degradation in water / sediment DT50 / 90 values	EFSA: LoEP Vol 1 p 116. Please indicate with an annotation that the DT values for water and sediment presented are dissipation values as observed in the study and not kinetically derived degradation values.	RMS: Agreed, LoEP will be updated	Addressed The LoEP has been updated (version dated July 2007).

PEC in surface water and in ground water (B.8.6)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(14)	Vol. 3, B.8.6.1, Predicted concentrations in surface water	Notifier: In the substance specific input data used for the surface water modelling calculations, DT_{50} water and DT_{50} sediment values are listed for pyriproxyfen and its metabolites. However, as it was not possible to calculate separate degradation rates for water and sediment based on the data from the water-sediment studies, we understand that mean DT_{50} values for the total water-sediment system were used by the RMS for water and sediment, rather than separate values, in accordance with FOCUS guidance. Please	RMS: The fact that the mean value from the water-sediment system degradation was used will be included.	Addressed RMS to consider in a corrigendum or amended DAR.

PEC in surface water and in ground water (B.8.6)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		consider revising the list of input parameters accordingly to reflect this.		
4(15)	Vol. 3, B.8.6.3, Predicted concentrations in groundwater	Notifier: In Table B.8.6.3-1, on page 386, the crop interception factor for cotton used in the PEC_{gw} calculations for pyriproxyfen and its metabolites should be 75%, rather than 40%, to be consistent with the calculations reported in the DAR. Please consider revising the crop interception factors and corrected dose values in this table.	RMS: Table 8.6.3-1 will be updated in a revised DAR	Addressed RMS to consider in a corrigendum or amended DAR.
4(16)	Vol. 3, B.8.6.1 PECsurface water	UK: While we support the use of the Dutch national model for calculation of PECsw from glasshouse uses, for illustrative purposes to identify a safe use, it should be noted that a different approach has been used here (i.e. for FOCUS Step 2 calculations after assuming a s surface water loading of 0.1% the results were divided by a factor accounting for the default drift value of 2.38%). We suggest the following statement should be added "However, MS.s may wish to consider the potential for surface water contamination in their own localities arising from glasshouse use"	RMS: Calculations were performed using the default drift values from FOCUSsw. The results were than corrected to assume a loading of 0.1% to the surface water. To achieve this the results were divided by 23.8. We can agree with the UK proposal to add such kind of sentence in case MS would like to choose a different approach for glasshouse uses. Probably not only in Vol.3 but also for the RA in Vol.1. Will be done in revised DAR or addendum.	Addressed RMS to consider in a corrigendum or amended DAR.
4(17)	Vol. 3, B.8.6.3, Table B.8.6.3-1	UK: Table 8.6.3-1 states 40% crop interception but text above it states 75% interception. Please clarify	RMS: Table 8.6.3-1 contains outdated data. 75% is the correct value for crop interception. Table will be updated in revised DAR.	Addressed RMS to consider in a corrigendum or amended DAR.

PEC in surface water and in ground water (B.8.6)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	PECgroundwater			
4(18)	Vol. 3, B.8.6.1/2, Predicted environmental concentrations in surface water and sediment. Vol 1 List of endpoints, PECsurface water & PECsediment	EFSA: On pages 377-378 of Volume 3 it is stated that DT50 in soil , maximum observed soil formation fractions and 50% crop interception were used to calculate PEC at step 2 of FOCUS for the glasshouse use patterns. These values were not used. When No runoff / drainage is selected (as was the case here) the PEC calculated do not use any of this soil information in the calculation. LoEP Vol 1 p 117-133. In line with this comment regarding Vol 3 the input values that are not used in the calculations for the protected uses should be deleted from the method of calculation and main routes of entry boxes. (Step 1 and 2 calculations for glasshouse use).	RMS: The mentioned values were put into the substance input sheet and are therefore listed. Since there are also uses where runoff and drainage are relevant all substance parameters are relevant. RMS: Agreed, non relevant input values will be deleted from the respective boxes.	Addressed The LoEP has been updated (version dated July 2007).
4(19)	Vol. 3, B.8.6.3, Predicted environmental concentrations in groundwater	EFSA: On pages 385-387 groundwater exposure assessments for pyriproxyfen or its metabolites 4-OH-Pyr and PYPAC are not presented for the applied for uses in glasshouses. An assessment is required as more than one protected crop can be grown per season and the application rate to the protected crops can be higher than for cotton. Therefore it is clear that the	RMS: Calculation for glasshouses were not performed as there is no FOCUS scenario available that is relevant for glasshouses. For NE 2 crops per season for tomatoes and eggplants is not relevant. Sometimes as surrogate for glasshouse use, field use is calculated. This could be done.	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 applied for uses in glasshouses. The applicant indicated that the requested clarification will be available by 01 December 2007.

PEC in surface water and in ground water (B.8.6)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	Vol 1 List of endpoints, PECgroundwater	available cotton calculations alone are not sufficient to cover the protected uses that require assessment. LoEP Vol 1 p 133-134. In line with this comment regarding Vol 3 the endpoints need to include information regarding the glasshouse uses on eggplant and tomatoes.		
4(20)	Vol. 1, Level 2, Appendix 3, List of endpoints	Notifier: On pages 119 and 127, the FOCUS Step 3 PEC_{sw} and PEC_{sed} values for cotton (actual and TWA) for pyriproxyfen are inconsistent with those reported in the DAR. Please check this and consider revising these values accordingly.	RMS: Correct. LoEP will be updated	Addressed The LoEP has been updated (version dated July 2007).
4(21)	Vol. 1, Level 2, Appendix 3, List of endpoints	Notifier: On page 120, please consider revising the water solubility of 4'-OH-Pyr used in the PEC_{sw} calculations to 1.4 mg/L and removing '(set to value parent)', to be consistent with the information reported in the DAR.	RMS: Correct. LoEP will be updated.	Addressed The LoEP has been updated (version dated July 2007).
4(22)	Vol. 1, Level 2, Appendix 3, List of endpoints	Notifier: On page 121, the FOCUS Step 1 24 h actual PEC_{sw} value for 4'-OH-Pyr should read as 0.3785 µg/L. Please consider revising this value in the list of endpoints.	RMS: Correct, typo. LoEP will be updated.	Addressed The LoEP has been updated (version dated July 2007).
4(23)	Vol. 1, Level 2, Appendix 3,	Notifier: On page 123, several of the	RMS: Correct, typo. LoEP will be updated.	Addressed

PEC in surface water and in ground water (B.8.6)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	List of endpoints	FOCUS Step 1 actual PEC_{sw} values for cotton for DPH-Pyr are inconsistent with those reported in the DAR. The Step 1 14-day TWA PEC_{sw} value should also be 0.0144, rather than 0.00144 µg/L. Please check this and consider revising these values accordingly.		The LoEP has been updated (version dated July 2007).
4(24)	Vol. 1, Level 2, Appendix 3, List of endpoints	Notifier: On pages 123 & 124 and 131 & 132, the DT_{50} soil for PYPAC used in the PEC_{sw}/PEC_{sed} calculations should be 37 rather than 36 days, to be consistent with the calculations reported in the DAR. Please consider revising this.	RMS: True. This will probably not have any consequences for PEC_{twa} values and the risk assessment.	Addressed The LoEP has been updated (version dated July 2007).
4(25)	Vol. 1, Level 2, Appendix 3, List of endpoints	Notifier: On page 125, several of the FOCUS Step 2 PEC_{sw} values for cotton (actual and TWA) for PYPAC are inconsistent with those reported in the DAR. Please check this and consider revising these values accordingly.	RMS: Correct. However this is only in the fourth digit. Changing the values will not influence the RA.	Addressed
4(26)	Vol. 1, Level 2, Appendix 3, List of endpoints	Notifier: On page 131, the FOCUS Step 2 7-day actual PEC_{sed} value for cotton for DPH-Pyr should be 0.1281, rather than 0.2181 µg/kg, to be consistent with the value reported in the DAR.	RMS: Correct, typo. LoEP will be updated	Addressed The LoEP has been updated (version dated July 2007).

PEC in surface water and in ground water (B.8.6)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		Please consider revising this.		
4(27)	Vol. 1, Level 2, Appendix 3, List of endpoints	Notifier: On page 133, several of the FOCUS Step 2 PEC_{sed} values for cotton (actual and TWA) for PYPAC are inconsistent with those reported in the DAR. Please check this and consider revising the values accordingly.	RMS: Correct. However this is only in the fourth digit. Changing the values will not influence the RA.	Addressed
4(28)	Vol. 1, Level 2, Appendix 3, List of endpoints	Notifier: On page 133, the crop interception factor for cotton used in the PEC_{gw} calculations for pyriproxyfen and its metabolites 4'-OH-Pyr and PYPAC, should be 75%, rather than 40%, to be consistent with the calculations reported in the DAR. Please consider revising this in the list of endpoints.	RMS: Correct. LoEP will be updated	Addressed The LoEP has been updated (version dated July 2007).

Fate and behaviour in air and PEC in air (B.8.7-8.8)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(29)	Vol. 1, Level 2, 2.5.4, Fate and behaviour in air Vol. 1, Level 2,	Notifier: The estimated Henry's Law Constant of pyriproxyfen at 22-25°C should be $<1.16 \times 10^{-2}$, rather than $<1.16 \times 10^{-5}$ Pa m^3 mol^{-1}. Please consider revising the DAR accordingly.	RMS: Correct, will be changed in revised DAR.	Addressed RMS to consider in a corrigendum or amended DAR.

Fate and behaviour in air and PEC in air (B.8.7-8.8)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	Appendix 3, List of endpoints Vol. 3, B.8.8, Predicted environmental concentrations in air (PECa)			
4(30)	Vol. 1, Level 2, 2.5.4, Fate and behaviour in air Vol. 3, B.8.8, Predicted environmental concentrations in air	Notifier: The reported DT_{50} for pyriproxyfen in air calculated using the Atkinson method (0.26 hrs) is inconsistent with the value reported by the RMS in the Physchem section (3.8 hrs). Please check this and consider revising the DAR accordingly.	RMS: Correct. LoEP will be updated.	Addressed RMS to consider in a corrigendum or amended DAR.
4(31)	Vol. 1, Level 2, Appendix 3, List of endpoints	Notifier: On page 134, the DT_{50} for pyriproxyfen in air, calculated using the Atkinson method (0.26 days) is inconsistent with the value reported by the RMS in the Physchem section (3.8 hrs). Please check this and consider revising the value in the list of endpoints accordingly.	RMS: Correct. LoEP will be updated.	Open point 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.
4(32)	Vol. 1, Level 2, Appendix 3, List of endpoints	Notifier: On page 134, the estimated Henry's Law Constant for PYPAC should be 2.00×10^{-4} Pa m^3 mol^{-1}, rather than 1.97×10^{-9} Pa m^3 mol^{-1}, to	RMS: Correct. LoEP will be updated.	Addressed The LoEP has been updated (version dated July 2007).

Fate and behaviour in air and PEC in air (B.8.7-8.8)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		be consistent with the value reported in the DAR. Please consider revising this.		

Definition of the residues (B.8.9)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(33)	Vol 1 List of endpoints, Definition of the residue	EFSA: LoEP Vol 1 p 134. Please quote all the residues for which an assessment is triggered. In this context the definition for groundwater should include: pyriproxifen, 4-OHPyr and PYPAC. Following current guidance an assessment is only triggered in soil for parent pyriproxifen. For soil the references to the metabolites should therefore be deleted.	RMS: Correct, will be updated in LoEP and revised DAR or addendum. For groundwater the 2 metabolites should be added to the residue definition.	Addressed The LoEP has been updated (version dated July 2007).

Other comments				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
4(34)	Vol. 2, Annex A.8 Environmental fate and behaviour	Notifier: For Annex Point IIIA 9.2.3/04, (Report No. NNP-0068), the study title should be 'PYPAC - Water solubility', rather than '4'-OH-Pyriproxyfen - Water solubility'. Please consider	RMS: Will be checked and updated.	Open point 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.

Other comments				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	Vol. 3, B.8.10, References relied on	revising this in the reference lists. Study Report No. NNP-0067, '4'-OH-Pyriproxyfen - Water solubility' has not been included in the reference lists, but is referred to in the DAR. Please consider adding this study to the reference lists.		(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.
4(35)	Vol 3 B.8.10 References relied on and the separate list of information tests and studies relied on.	EFSA: Vol. 3 page 391 and the separate list of information tests and studies relied on: Please delete Fathulla 1995a (anaerobic aquatic metabolism). There is no data requirement for this study type and it is not relied on in the exposure / risk assessment.	RMS: Agreed, will be deleted.	Open point RMS to delete the reference Fathulla 1995a (anaerobic aquatic metabolism) from the separate list of information tests and studies relied on.
4(36)	Vol 3 B.8.10 References relied on and the separate list of information tests and studies relied on section for fate and behaviour.	EFSA: Vol. 3 pages 394-5 and the separate list of information tests and studies relied on: Please delete all the annex III references (References for the plant protection product) as none of these reports (calculations) are summarised in the DAR or referred in the DAR. Therefore they cannot have been relied on. The calculations in the DAR would appear to be those carried out by the RMS and not those provided by the applicant?	RMS: Agreed partially. All PECs were recalculated by RMS with notifiers calculations as supplementary information. However not all references mentioned under the list 'references for plant protection product' are PEC calculations, therefore deleting them all would result in large omission in the list of references relied on. We will update the list.	Open point 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.

Rapporteur:

Comments received on reporting table, section Environmental fate and behaviour (B.8)			
Reference to reporting table	MS / Notifier	Comment	EFSA response
4(6)	NL	We don't agree on the open point set. According to FK 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 not a true degradation rate. The only wording suitable to add would be 'worst case estimate'.	This DT50 represents an observed decline and not degradation. The endpoints need to make this clear. The wording of the open point has been amended in line with the agreed wording for the analogous situation that was pertinent to metabolites of fenpyroximate that was agreed at PRAPeR 32.
4(7)	UK	Given the estimated pKa value for pyriproxyfen (pKa 6.87) and the chemical structure for metabolites 4'-OH-Pyr and PYPAC, the batch equilibrium studies should have been conducted with a wider pH range of soils and for parent, at least one soil of pH <6, (the range tested was pH 7-8 for parent and 6.9-7.9 for metabolites). Therefore, the UK considers pH dependency of adsorption cannot be ruled out for parent compound or these two metabolites and the statement in the DAR and LoEPs "*No pH dependency of adsorption at the environmental relevant pH range is expected*…" should be amended accordingly, (unless it is possible to justify that soils of pH <7 will not be exposed in practice). The UK agrees that 3 soils is too small a dataset upon which to conclude whether or not there is a trend for pH dependency for the two metabolites, (though this might be expected based on their structure). However, given that the Koc values in Table B.8.2.3-1 for parent are high and range from 11000-34200 L/kg (i.e. non-mobile), it is unlikely that assuming stronger adsorption for acidic soils instead of the mean Koc (21175 L/kg) in groundwater modelling would have much impact on the results (which were PECgw <0.001 µg/L). For the metabolite PYPAC, which is predicted to be moderate to very mobile, the Koc value of 9 L/kg for clay loam should perhaps have been used in groundwater modelling instead of the mean Koc of 20.7 L/kg, but given the current results	Noted original proposal of addressed, RMS to provide the clarification in column 3 in a corrigendum or revised DAR has been amended to a: Point of clarification for the applicant.

Comments received on reporting table, section Environmental fate and behaviour (B.8)			
Reference to reporting table	MS / Notifier	Comment	EFSA response
		(PECgw <0.001 µg/L) it is not expected that this would significantly impact on the risk assessment. For the metabolite 4'-OH-Pyr, again possibly the Koc of 921 L/kg for clay loam should have been used in the groundwater modelling instead of the mean Koc 2598 L/kg, but given the PECgw is estimated as <0.001 µg/L, it is not expected that this would significantly impact on the risk assessment.	
4(7)	NL	The 2 metabolites formed in soil at >5% at 2 consecutive time points are 4-(4-Hydroxyphenoxy)phenyl (*RS*)-2-(2-pyridyloxy)propyl ether (4'-OH-PYR) and (*RS*)-2-(2-Pyridyloxy)propionic acid (PYPAC). 4'-OH-PYR will not dissociate so pKa and pH dependency are not relevant. The pKa for the propionic acid can be estimated to be around 4. (LogKow Estimated Log P: 1.35) A pH dependency of this metabolite can be relevant. Nevertheless, based on the few data available, all for soils where PYPAC will be present in the dissociated form, a clear relationship cannot be derived. For acid soils the values may not apply.	Noted original proposal of addressed, RMS to provide the clarification in column 3 in a corrigendum or revised DAR has been amended to a: Point of clarification for the applicant.
4(7)	NOT	It is not possible to draw any clear conclusions concerning the influence of pH on the adsorption of 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)]. Notifier can submit this available information. Proposed submission date: 01 December 2007.	Noted original proposal of addressed, RMS to provide the clarification in column 3 in a corrigendum or revised DAR has been amended to a: Point of clarification for the applicant. The proposed date of submission has been added to the reporting table.
4(7)	DE	DE supports the view of EFSA that a pka-value for the two metabolites would be helpful to assess if a correlation between kf and pH is likely. In general, it is nearly impossible to find a significant correlation with just three data points, which would make further measurements to cover a wide range of pH-values valuable for the assessment. If no further data and information	Noted original proposal of addressed, RMS to provide the clarification in column 3 in a corrigendum or revised DAR has

Comments received on reporting table, section Environmental fate and behaviour (B.8)			
Reference to reporting table	MS / Notifier	Comment	EFSA response
		would be provided a supposable solution of this problem could be to assume a correlation between kf and pH and to select the worst case Koc values for the risk assessment of the two metabolites.	been amended to a: Point of clarification for the applicant.
4(9)	NL	Agree on open point. Recalculate PECs for metabolite 4-OH Pyr in tomato/eggplant considering 2 crops per year and present these in an addendum.	Noted
4(19)	NOT	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 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, a worst-case groundwater modelling assessment for pyriproxyfen and its metabolites 4'-OH-Pyr and PYPAC will be conducted to cover the glasshouse uses in Southern Europe. The simulations will be 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. Proposed submission date: 01 December 2007	Noted The proposed date of submission for the new modelling has been added to the reporting table.
4(19)	NL	Agree on data requirement for PECgw and greenhouse use.	Noted

Rapporteur:

Comments received on reporting table, section Environmental fate and behaviour (B.8)			
Reference to reporting table	MS / Notifier	Comment	EFSA response
4(31)	NL	Agree on open point. To be brought in line with FCE section.	Noted
4(34)	NL	Agree on open point	Noted
4(35)	NL	Agree on open point	Noted
4(36)	NL	Agree on open point.	Noted

5. Ecotoxicology

Birds and mammals (B.9.1 and B.9.3)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(1)	Vol. 1, Level 2, 2.6.1, Effects on terrestrial vertebrates (page 54); Vol. 1, Level 2, Appendix 3, List of endpoints; Vol. 3, B.9.1.3 (page 403 and 404)	Notifier: Regarding the Daily doses for the reproductive toxicity studies, they are calculated for each sex in the DAR. However, the Daily doses separated sex-by-sex are not considered meaningful, because birds were housed with one male and one female per pen throughout the studies and hence the feed consumptions were only the mean values for pairs (i.e. not specific values for each sex). Thus, the Daily doses for mallard and bobwhite reproductive toxicity studies should be 73.8 and 83.8 mg a.s./kg bw/day, respectively.	RMS: Food consumption is never measured individually in reproduction studies, but always for pairs or groups. As a worst case, NL will use the lowest value for the separate sexes. 70.2 mg/kg bw/d will be used for the risk assessment.	Addressed
5(2)	Vol. 1, Level 2, Appendix 3, List of endpoints	Notifier: It is not clear why two NOEC values have been given for the reproductive toxicity to birds endpoints (for the two species tested, mallard duck and bobwhite quail). In the case of the dietary toxicity to birds, the single worst-case endpoint has been given for the two species tested.	RMS: Highest endpoint will be removed from LoEP.	Addressed

Rapporteur:

Birds and mammals (B.9.1 and B.9.3)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(3)	Vol. 3, B.9.1.5.1, Risk of active substance to birds	EFSA: We agree that the risk from intake of contaminated drinking water could be assessed based on PEC surface water for the glasshouse uses. However, for field use exposure from intake of diluted spray solution in leaf axils or from puddles should be considered.	RMS: Will be done in the addendum.	Open point RMS to include a risk assessment for birds and mammals from uptake of contaminated drinking water in an addendum.
5(4)	Vol. 3, B.9.1.5.2 (page 411)	Notifier: Concerning DPH-Pyriproxyfen, the value of “hen: 4.1% AR” cannot be traced. It is estimated the value as “hen: 3.5% AR” (i.e. 3.5% = (2.2% + 5.8%) / 2 x (84% + 89.5%) / 2)).	RMS: Two residue studies with chicken are available. DPH-PYR has been found in both these studies. Studie 1: 89.5% AR with 5.4 and 5.8 TRR on day 3 and 7, respectively: 3.1 AR DPH-PYR.. Studie 2: 84 % AR with 2.2 and 5.2 TRR on day 3 and 7, respectively: 5.0 AR DPH-PYR.. On average this gives a value of 4.1% AR DPH-PYR . This information will be included in the revised DAR.	Addressed RMS to include the clarification on the 4.1% AR DPH-Pyriproxyfen for hen in a revised DAR.

Aquatic organisms (B. 9.2)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(5)	Vol. 1, Level 2, Appendix 3, List of endpoints	Notifier: In the table of toxicity/exposure ratios for aquatic organisms no values have been given for fish algae and	RMS: The LoEP will be revised.	Open point RMS to include the TER values for fish, algae and Lemna in the LoEP.

Aquatic organisms (B. 9.2)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		Lemna (although it is stated that the TERs given are for the most sensitive aquatic organisms i.e. aquatic invertebrates). In the case of the long-term TER values (cotton) a timescale of 21 d has been given (i.e. for the *Daphnia* chronic toxicity study) but the endpoint used is actually from the microcosm study (56 d duration). The Annex VI trigger (10) given for the long-term TER value (cotton) is based on the use of the *Daphnia* chronic toxicity endpoint but as it is actually based on a higher tier microcosm study the trigger should be lower. In the DAR it is set at 1 i.e. the NOEAEC and EAC are the same, allowing direct comparison with the PEC. The comparison of the surface water PEC values for the tomato/eggplant use with the cotton use should point out that the former is FOCUS Step 2 and the latter FOCUS Step 3 i.e. the comparable difference will be larger resulting in an even bigger safety margin for tomato/eggplant. A long-term TER value of 130 could be calculated for the tomato/eggplant use		See also comment 5(9)

Aquatic organisms (B. 9.2)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		using the microcosm EAC (5.0 μg a.s./L).		
5(6)	Vol. 1, Level 2, Appendix 3, List of endpoints	Notifier: In the bioconcentration table, the level of residues (%) in organisms after the 14 day depuration period should be ≤10.4% (or rounded to 10%) rather than ≤11%.	RMS: Ok, will be revised in LoEP.	Open point RMS to amend in the LoEP the level of residues after 14d depuration phase.
5(7)	Vol. 1, List of endpoints, Bioconcentration	The level of residues at 14 days was reported as 10.4% in the study (and not <11%).	RMS: will be changed in LoEP.	See open point 5(6)
5(8)	Vol. 1, List of endpoints, TER for aquatic organisms	EFSA: It is not clear from the LoEP that the TER of 123 for *Daphnia* is calculated with a PEC_{sw} based on FOCUS Step 1.	RMS: will be clarified in LoEP.	Open point RMS to clarify in the LoEP the PECsw values used in the TER calculations for aquatic organisms
5(9)	Vol. 1, List of endpoints, TER for aquatic organisms	EFSA: Please report TER values for fish calculated with PEC from FOCUS steps and LC_{50}/NOEC from laboratory studies since fish is not covered by the microcosm study.	RMS: will be added to LoEP.	See open point 5(5)
5(10)	Vol.1, Level 3, cover page (page 141)	Notifier: 'Safety phrase: S60, S61' should not appear on page 141. The document should be re-formatted such that the safety phrases appear on the previous page (page 140).	RMS: We will do this in the revised DAR.	Addressed

Rapporteur:

Aquatic organisms (B. 9.2)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(11)	Vol 3, B.9.2.1., acute toxicity to aquatic life	UK: Helpful summary tables of the studies, very clear and all that is necessary for acute studies done to guideline and GLP.	RMS: Thanks.	Addressed RMS to include in the study summaries in future DARs all details which are required for a transparent and comprehensible evaluation of the endpoints (e.g. tested concentrations and effects observed at each concentration, details on the statistical evaluation of the endpoints)
5(12)	Vol.3, B.9.2.1.1, Acute toxicity of the active substance	EFSA: Since initial measured concentrations in the acute toxicity studies with aquatic organisms were <80% of nominal in all cases but one, toxicity values should be expressed as initial measured concentrations according to the recommendations in the GD on aquatic ecotoxicology.	RMS: The GD states: 'if measured concentrations in semi-static and flow-through systems fall graduately below 80% during the test, then toxicity values should be expressed as mean measured concentrations'. Therefore we have expressed the results of the flow-through and semi-static tests with the a.s. and 4-OH-pyriproxyfen as m.m. In the static tests with the formulation and PYPAC, the test substance did not break down fast. In such a case, we feel that it is appropiate to express the endpoints in mean measured concentrations, just like in the semi-static and flow-through tests. We do not really understand why the Guidance Document makes a distinction here.	Addressed

Aquatic organisms (B. 9.2)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(13)	Vol. 3, B.9.2.2.1.4, Microcosm and mesocosm studies	EFSA: On p. 435, the last sentence, it is stated that recovery of Cladocerans was observed on day 28 while in Table B.9.19 a significant reduction is indicated also on day 28. Please clarify.	RMS: On sampling day 28 the NOEC for *Cladocera total*was 0.32 ug a.i./L. At this time point, however, abundance values at higher concentrations were similar to those seen at the 0.02 ug a.i./L-treatment level. Therefore, this statistical outcome was not based on a clear concentration-response relationship and occurred only late in the experiment. The outcome is considered not to be treatment related.	See open point 5(17)
5(14)	Vol. 3, B.9.2.2.2.3 (page 437)	Notifier: In the *Chironomus* study with pyriproxyfen, 4'-OH-Pyr and PYPAC were observed in the test media and so the risk assessment based on the results obtained also applies to these metabolites.	RMS: That might be true. However, since no metabolite was found in a concentration >10% in sediment, no data are required. DAR will not be revised on this point.	Addressed
5(15)	Vol. 3, B.9.2.3.1.1, Acute risk to aquatic organisms (page 441)	EFSA: It was noted that the acute risk to *Daphnia* was calculated with PEC_{sw} based on FOCUS Step 1 which includes also 10% drift and run-off input. The header to Table B.9.20 says PECs based on 2.77% spray drift which is confusing.	RMS: We agree that this is confusing. The following input parameters were used: in Step 1, 2.77% spray drift + 10% run-off and drainage; in Step 2, 2.77% drift + 3% run-off and drainage; in Step 3, 2.77 % spray drift + drainage dependent on substance characteristics. This will be clarified in the revised DAR.	Addressed RMS to clarify the PECsw values used in the TER calculations in a revised DAR.

Aquatic organisms (B. 9.2)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(16)	Vol. 3, B.9.2.2.3.1.2 (page 442)	Notifier: In the aquatic invertebrate risk assessment for pyriproxyfen, it is considered that TWA-PECs may be applicable for the risk assessment based on the recovery potential demonstrated in the recovery test with *Daphnia pulex* and limitation of acute effect (only at the highest level, 20 ppb) in the microcosm study. Therefore, Notifier would suggest that the section dealing with the use of time-weighted-average concentrations in the 2nd paragraph, i.e. “Refinement using 21-day TWA……..exposure occurring early on in the exposure period” could be reviewed.	RMS: Considering the fast degradation of the active substance and the fact that we cannot exclude that the transient effect seen on Daphnia galeata in the microcosm study is caused by the pulsed application, we think using PECtwa’s is inappropiate.The recovery test is done with another Daphnia species and cannot be used for Daphnia galeata. The text of the DAR will not be revised.	Addressed
5(17)	Vol. 1, Level 2, 2.6.2, Effects on aquatic species, Risk assessment: Vol. 1, Level 2, Appendix 3, List of endpoints; Vol. 3, B.9.2.2.1.4 (page 436);	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 to set NOEAEC of 20 µg a.s./L.	RMS: Considering the fact that no recovery was shown for one species at 20 ppb, RMS thinks the NOEAEC should be 5 ppb.	Open point 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 also comments 5 (13), 5(19), 5(20), 5(21)

Rapporteur:

Aquatic organisms (B. 9.2)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
	Vol. 3, B.9.2.3.1.2 (page 443)			
5(18)	Vol. 1, Level 2, 2.6.2, Effects on aquatic species, Table 2.6.2-10; Vol. 3, B.9.2.3.1.2, Tables B.9.25 (page 443) and B. 9.25 (page 444)	Notifier: For the calculation of refined long-term TERs for pyriproxyfen, a FOCUS Step 3 surface water PEC value of 0.393 μg a.s./L has been used (resulting from 1.6% drift over 1.3 m). This drift value is inconsistent with the previous tables, where the standard default drift distance for field crops of 1 m has been used (2.77% drift). 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). Note also that the table on page 444 (Vol. 3, B.9.2.3.1.2) should be renumbered to B.9.26.	RMS: We agree that the drift value in the table is confusing. Drift percentage is still 2.77% in Step 3. The value mentioned, 1.6, is the aeric mean mass deposition, expressed as percentage of the application rate. In the revised DAR, 1.6 will be changed into 2.77%. 1.3 m is the standard distance to the crop in Step 3, D6, ditch. This will be clarified with a note in the revised DAR. The PECsw will be changed to 0.381 in the revised DAR (this change does not influence the outcome of the risk assessment). The two tables B.9.25 will be renumbered 29a and 29b in the revised DAR.	Open point RMS to recalculate in an addendum the TERs for aquatic organisms with the corrected PECsw.
5(19)	Vol. 1, Level 2, 2.6.2, Effects on aquatic species, Risk assessment: Vol. 3, B.9.2.3.1.2 (page 444)	Notifier: On page 64, when discussing the refined long-term risk assessment for pyriproxyfen, it is stated that the long-term TER based on the EAC from the microcosm study is above the Annex VI trigger of 10. However, this trigger value applies to the long-term TER values obtained with single	RMS: Agree that trigger of 10 is incorrect, will be corrected in the revised DAR.	See open point 5(17)

Aquatic organisms (B. 9.2)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		species laboratory chronic toxicity studies (fish and *Daphnia*). The HARAP guidance document (1999) indicates that microcosms should be assessed on a case by case basis, with the possibility of using the EAC directly in the risk assessment without an uncertainty factor. This is indicated in Vol. 3, B.9.2.3.1.2, page 444.		
5(20)	Vol. 3, B.9.2.3.1.2, Long-term risk (of the as for aquatic organisms)	DE: Although there is a factor of more than 300 between the laboratory endpoint (NOEC = 0.015 µg as/L) and the result of the microcosm study (NOEAEC = 5.0 µg as/L), the conclusions of the RMS can generally be supported. However, the RMS is kindly asked to provide a justification for a) equalizing the $NOEAEC_{MICRO}$ with an EAC and b) setting the trigger value to 1 without any safety margins.	RMS: It concerns a reliable study. We agree that a safety factor of three would be necessary for an NOEAEC based on significant effects with recovery within 8 weeks. In this case however, the 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. Therefore, we consider a safety factor not necessary.	See open point 5(17)
5(21)	Vol. 3, B.9.2.3.1.2, Acute risk to aquatic organisms	EFSA: It was noted that it was proposed that no assessment factor is needed for the microcosm study. We do not agree to this and propose that this is discussed in an experts meeting.	RMS: See answer to DE above: we consider a safety factor not necessary. However, we agree to discuss this in an expert meeting.	See open point 5(17)

Bees and non-target arthropods (B. 9.4 and B.9.5)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(22)	Vol. 1, List of endpoints, toxicity to bees	EFSA: LD_{50} values from non acceptable studies should not be included in the LoEP.	RMS: Agreed. The endpoints for the a.s. from the studies by Hoberg will be removed if no further information is given by the notifier about the comparability of the a.s. used in the study to technical pyriproxyfen.	Open point RMS to delete the LD50 values for bees from studies which are considered not acceptable
5(23)	Vol. 3, B.9.4.1.2.1 (page 454)	Notifier: It is stated that in study 2 (a bumble bee brood test) the methods deviated from the current guideline (EPPO, 2002). However, this guideline is for honey bee brood and there is currently no validated test guideline for bumble bee brood.	RMS: It is true that there is no standard guideline for bumblebees yet. However, until one is developed, following the guidelines for honeybees is the best alternative. The study was rejected on the basis of general apects, which, although prescribed in EPPO 2002, are not specific for honeybees but can logically be applied to bumble bee studies as well.	Addressed
5(24)	Vol. 3, B.9.4.1.3 (page 455)	Notifier: The guideline requirements referred to by the RMS in the residue study (EPPO, 2000) are for a laboratory acute toxicity test. It does not include requirements for a residual toxicity study.	RMS: Indeed EPPO does not give specific guidance for a residue study. However, the general guidance for bee studies can still be followed. In all types of toxicity studies it must be proven that exposure has taken place, which in this case was not clear because no toxic standard was included and no mortality was seen in the treatment group. In the revised DAR, the text will be changed to clarify this.	Addressed RMS to include the explanation from column3 on the exposure in the proof of exposure in a revised DAR.

Bees and non-target arthropods (B. 9.4 and B.9.5)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(25)	Vol. 1, Level 2, 2.6.3, Effects on bees and other arthropod species (page 68); Vol 3, B.9.4.2.3 (page 459)	Notifier: The rate of 124 g a.s./ha in 95 L water is equivalent to 1305 mg a.s./L. This means that the concentration of test solution is significantly higher than those of application solutions for tomato/eggplant in southern Europe greenhouse (i.e. 50-75 mg a.s./L). This should be noted.	RMS: It is true that the concentration in the spray liquid was much higher in the brood test than in the proposed use in S-Europe. This will be added in the revised DAR. However, the study is still unacceptable.	Addressed
5(26)	Vol. 1, Level 4, Demand for further information, 4.9 Ecotoxicology; Vol. 3, B.9.4.1.1 (page 449) and B.9.4.2.1 (page 458)	Notifier: Additional information is required to accept the study data obtained in the honey bee acute toxicity study by Hoberg J.R. (2001). According to the 5 batch analysis and the specification defined in the dossier (Document J Specification No. 01), the tested sample is in a range of technical grade of pyriproxyfen and study should be valid. It is made clear that this is not required for Annex 1 inclusion. In addition, in Volume 3, Annex B.9.4.4.1 it states that further studies are not needed since acceptable data for the toxicity of the formulation to honey bees are available.	RMS: See new data gap at 5(39).	See data requirement 5(39)

Bees and non-target arthropods (B. 9.4 and B.9.5)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(27)	Vol. 1, Level 2, 2.6.3, Effects on bees and other arthropod species (page 68); Vol. 1, Level 3, 3.1 Background to the proposed decision (page143); Vol. 1, Level 4, Demand for further information, 4.9 Ecotoxicology; Vol 3, B.9.4.2.3 (page 459)	Notifier: The bee brood risk assessment indicates that the rate used in the field study (75 g a.s./ha) was too low to address the risk due to exposure on tomato and egg plant in Southern Europe (1-2 X 112.5 g a.s./ha). This is a protected (glasshouse) use where the main risk is to bumble bees used for commercial glasshouse pollination. Exposure to honey bees will be extremely low and bumble bees are currently not addressed at Annex I. It is not appropriate for this to be included as an Annex I data requirement, rather it should be addressed at Member State level as indicated in the DAR.	RMS: As stated in the DAR, we agree that this can be seen as a MS-issue. We feel that this has been stated clearly in all volumes, except from Vol. 1, level 3, 3.1. We will change the sentence about the ecotoxicological risks to clarify that the risk to bee brood is unresolved.	Addressed
5(28)	Vol. 3, B.9.4.2.3, Risk to bee brood (page 459)	EFSA: We agree to the data requirement for the applicant to address the risk to bee brood for the use in tomato and egg plant in Southern EU.	RMS: Ok.	Data gap Applicant to address the risk to bee brood for the use in tomato and egg plant in Southern EU.

Rapporteur:

Bees and non-target arthropods (B. 9.4 and B.9.5)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(29)	Vol.3, B.9.11, List of references relied on	EFSA: Since the study by Hoberg (2001) on acute toxicity of pyriproxifen to bees was no accepted it should be deleted from the list of references relied on.	RMS: Agreed. The reference from the study by Hoberg will be removed from the revised DAR if no further information is given by the notifier about the comparability of the a.s. used in the study to technical pyriproxyfen.	Addressed RMS to delete the study of Hoberg (2001) on acute toxicity of pyroxifen to bees since it was considered as not acceptable.
5(30)	Vol. 1, Level 2, 2.6.3.2, Other arthropod species, Table 2.6.3.2-1; Vol. 1, Level 2, Appendix 3, List of endpoints; Vol. 3, Table B.9.40	Notifier: Concerning the ER50 value for *Aphidius rhopalosiphi*, the regression analysis should be conducted with careful data handling. In this study, since the lowest dose (31.25 g a.s./ha) is lower than the NOER (62.5 g a.s./ha) and then out of dose-effect relationship range (62.5-125 g a.s./ha), this rate should not be included in the regression analysis for ER50 evaluation. Based on this, an ER50 value of 92 g a.s./ha seems to be more appropriate.	RMS: The possibility that the effect seen at the lowest dose is treatment related cannot be excluded. The ER50 of 81 g a.s./ha will not be changed.	Open point MSs to discuss in an expert meeting the ER50 calculation for *A. rhopalosiphi*.
5(31)	Vol. 1, Level 2, 2.6.3, Effects on bees and other arthropod species, Table 2.6.3.2-2; Vol. 3, Table B.9.42	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	RMS: Values will be checked and revised if necessary when we revise the DAR.	Open point RMS to check and revise the HQ values for *A. rhopalosiphi* and *Orius laevigatus* in a revised DAR.

Bees and non-target arthropods (B. 9.4 and B.9.5)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
		the uncertainty factor of 10 rather than multiplied).		
5(32)	B.9.5.3: Risk assessment for non-target arthropods (page 463)	UK: Whilst the principle of the risk calculations proposed by the RMS is understood, it is noted that the standard ESCORT 2 HQ procedure and triggers were only validated for Tier 1 glass slide tests on *A. rhopalosiphi* and *T. pyri* and only using 'typical' contact toxins. We feel that, given the mode of action and route of uptake of pyriproxyfen, there should be some further discussion over the relevance of the standard suite of studies in terms of species used, life stages, route of uptake, duration - and whether they are indeed fully able to address the exposure and risks from such an IGR	RMS: 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 appropiateness 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.	Open point 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.

Earthworms and other soil non-target organisms (macro and micro) (B. 9.6, B.9.7 and B.9.8)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(33)	Vol.1, Level 2, Appendix 3, List of endpoints: Vol. 1, Level 4, Demand for further information, 4.9 Ecotoxicology; Vol. 3, B.9.8 (page 470)	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 with the DAR response 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.	RMS: Study will be included in the addendum.	Data gap Applicant to submit the studies on effects of technical pyriproxyfen on soil respiration and nitrification.
5(34)	Vol. 2, A.9, Ecotoxicology Vol. 3, B.9.11, References relied on	Notifier: A new study (Report No. NNW-0178) submitted in January 2006 should be added in the reference lists.	RMS: Study will be included in the addendum.	Data gap The new study Report No. NNW-0178) submitted in January 2006 should be evaluated in an addendum.
5(35)	Vol.3, B.9.7	EFSA: We agree to the data requirement for a new study on effects on soil nitrogen turnover and respiration.	RMS: A new study is available and will be included in the addendum.	See data requirement 5(33)

Other non-target organisms (flora and fauna), sewage treatment (B.9.9 and B.9.10)				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(36)	Vol. 1, Level 2, Appendix 3, List of endpoints	Notifier: In the table for other non-target organisms, the conclusion for the plant screening data that pyriproxyfen shows no herbicidal activity, should be added (as for insecticidal and fungicidal activity).	RMS: Screening data on plants are already included in the LoEP.	Addressed

Other comments				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(37)	Vol. 1, List of endpoints, General	EFSA: Please use the EPCO No E 4, revision 4 (September 2005) template for the list of endpoints.	RMS: This will be done when we write the addendum.	Open point RMS to use the EPCO No E 4, revision 4 (September 2005) template for the list of endpoints when the LoEP is revised.
5(38)	Vol. 3, B.9, background information	EFSA: The background information and the table with an overview of metabolites are very much appreciated.	RMS: Thank you!	Addressed

Other comments				
No.	Column 1 Reference to DAR (vol., point, page)	Column 2 Comments from Member States or applicant	Column 3 Evaluation by (RMS) rapporteur and - if available - (Co-RMS) Co-rapporteur	Column 4 Data requirement or Open point (if data point not addressed or fulfilled)
5(39)	Vol. 3, B.9 General	EFSA: A full specification of the material used in all studies should be provided by the applicant and the compliance with the specification of the technical material should be assessed.	RMS: Agreed. Data gap: the notifier must 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.	Data requirement 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.

Comments received on reporting table, section Ecotoxicology (B.9)			
Reference to reporting table	MS / Notifier	Comment	EFSA response
5(3)	NOT	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, a worst-case assessment can be conducted for exposure from uptake of diluted spray solution in leaf axils or from puddles, according to the guidance provided in SANCO/4145/2000. Notifier can submit this information. Proposed submission date: 01 December 2007.	
5(18)	NL	We think it is not necessary to present new TER-values in an addendum, since the PECs change only slightly and there will be no influence on the outcome of the risk assessment. We propose to address this in the revised DAR.	
5(28)	NOT	The 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,	

Rapporteur:

Comments received on reporting table, section Ecotoxicology (B.9)			
Reference to reporting table	MS / Notifier	Comment	EFSA response
		and to conform with national risk management procedures and associated label phrases.	
5(32)	NOT	The 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 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).	
5(32)	NL	We would like to rephrase this open point to "MSs to discuss in an expert meeting whether the risk to non-target arthropods is sufficiently addressed considering the particular mode of action of IGR's such as pyriproxyfen", to emphasise that this discussion should have a broader context than just pyriproxyfen.	
5(33)	NOT	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 (see also Comments 5 (34) and 5 (35)).	
5(39)	NOT	Details of specifications of the formulations and the compliance of the used materials specifications with the specification of the technical material will be provided. Proposed submission date: 01 December 2007.	