PEER REVIEW REPORT ON **FLUOXASTROBIN** 15.08.2005

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Comments on the Draft Assessment Report (DAR) on fluoxastrobin

End of commenting period: 09.01.2004 (NOT), 27.01.2004 (MS)

Date	Supplier	File
16.12.2003	Germany	01 fluoxastrobin comments DE.doc
06.01.2004	The Netherlands	02 fluoxastrobin comments NL.doc
09.01.2004	Notifier	03 fluoxastrobin comments NOT.doc
21.01.2004	Denmark	04 fluoxastrobin comments DK.doc
03.02.2004	Sweden	05 fluoxastrobin comments SE.doc
20.02.2004	EFSA	06 fluoxastrobin comments EFSA.doc

2. Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	Volume 1, level 4, 4.1.6 Toxicology and metabolism, page 42	DE: The data requirement (In vitro genotoxicity on M 48) mentioned in Volume 1, level 4, 4.1.6. Toxicology and metabolism is supported.	The results of these studies are needed before a decision on possible inclusion in Annex I can be taken.
(2)	Volume 1, level 2, 2.3.1. page 18, “Need for further toxicological information” and Volume 1, level 4, 4.2.6 Toxicology and metabolism, page 43	DE: The data requirements mentioned in Volume 1, level 4, 4.2.6. are considered to be essential for the Annex-I inclusion, since only high purity (>98 %) batches have been tested for mutagenicity in bacteria and for skin sensitisation so far. Therefore, these data requirements should be moved to Volume 1, level 4, 4.1.6. Toxicology and metabolism.	In vol. 1, level 2 chapter 2.3.1 a further Ames test with the final production batch of fluoxastrobin and the evaluation of the toxicological significance of impurities in fluoxastrobin for skin sensitisation are proposed. These requirements were considered to be **not** essential for the Annex-I inclusion by the RMS and therefore included in Volume 1, level 4, 4.2.6. Toxicology and metabolism (Data which should be required and evaluated at MS level). However, the above mentioned studies should be repeated using the technical active substance with the proposed specification (minimum purity ≥ 910 g/kg) and evaluated by the RMS before Annex I inclusion .
(3)	Volume1, Appendix 1.2 Listing of end points, long term toxicity and carcinogenicity and Vol. 3, B.6.5.1	DE: The RMS should comment on possible influences of fluoxastrobin on the female endocrine system (i.e. possible treatment related effects on both increased incidence of uterus adenocarcinomas **and** uterine glandular hyperplasia). In view of the relevance to man the mechanism should be clarified and/or a classification of fluoxastrobin should be considered.	The incidence of uterus adenocarcinomas was statistically significantly increased. The RMS concluded that this was not a substance-related carcinogenic effect. However, the range of the historical control is not the only criterion for the biological relevance of an increased tumour incidence. The incidence of the adenocarcinomas in the uterus is significantly increased from 3/50 animals in the control group to 10/49 animals in the highest dose group **and** furthermore, the incidence of uterine glandular hyperplasia is also clearly increased from 1/50 to 6/49. A common (e.g. endocrine) mechanism of both findings can not be excluded.

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(4)	Volume1, Appendix 1.2 Listing of end points; Volume 1, level 2, 2.3 Impact on human and animal health and Vol. 3, B.6.3.3 and B.6.3.6	DE: The lowest relevant oral NOAEL/NOEL of short term toxicity is 1.5 mg/kg bw/d based on the 1yr dog study **and** the (second) 90 day dog study.	Obviously there is a discrepancy between assessment of the effects in oral short term dog studies and the final conclusions (AOEL derivation). The decreased body weight gain in males is considered to be a significant and toxicologically relevant effect by the RMS. (page 105 in Vol, 3, Annex B.6: "the RMS considers the decreased weight gain at all dose levels in males to be toxicologically significant"; page 120:"Reduced body weight gain was a key finding in dog studies"). In table B 6.21 the following NOAELs were set: 90-day dog: 1.5 mg/kg bw/d (Jones and Hastings 2001) 1-year dog: 1.5 mg/kg bw/d (Jones and Hastings 2002)
(5)	Volume 1, point 2.3.4 AOEL	DE: A new AOEL (systemic) of 0.015 mg/kg bw/d (1-yr **and** 90 day dog, SF: 100) is proposed.	The dose level of 3 mg/kg bw/d is not a NOAEL, but a LOAEL based on the decreased weight gain in male dogs (see table B 6.21). Therefore the dose level of 1.5 mg/kg bw/d should be used as basis of the AOEL.
(6)	Vol. 1, App. 3, Listing of endpoints, Chapter 2.3, Annex IIIA, point 7.3 (Acceptable exposure scenarios)	DE: On the basis of the new proposed systemic AOEL of 0.015 mg/kg bw/d, the operator exposure would also be acceptable.	DE has performed a operator exposure risk assessment according to the German model with the new AOEL.

section 1 - Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis (B.1-B.5)

1. Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis (B.1-B.5)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.2, general	No indications which studies are under GLP and which not.	
(2)	Vol. 1, list of endpoints	*purity should be staed of melting poit, boiling point, appearance and relative density	
(3)	Vol1, 1.3.5 and Vol. 3, B.1.1.5, CAS, EEC and CIPAC numbers	CIPAC number of Fluoxastrobin is 746 (also in list of endpoints)	
(4)	Vol. 3, B.2.1.2, boiling point	Purity is not stated (also in list of endpoints)	
(5)	Vol. 3, B.2.1.7/8/9, appearance	Studies should be carried out with technical material (96 %)	
(6)	Vol. 3, B.2.1.13, partition co-efficient	pH should be mentioned (also in list of endpoints)	
(7)	Vol. 3, B.2.1.15, hydrolysis rate	EPA guideline 161-**1**	
(8)	Vol. 3, B.2.2.12, viscosity	The shear rate should be mentioned in the case of the dynamic viscosity	
(9)	Vol.3, B5.1.1 and B5.1.3	The methods of analysis if the active substance in the technical active substance and the ppp should be discussed in Vol. 3 as this is not confidential	

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No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(10)	Vol.3, B5.2/3/4 Table B.5.2	-The linearity of the methods is missing -It is not clear what the temperature and humidity are of the air used for the validation. -The specificity of the residue method for air is missing -Soil source and types are not specified -It would be more clear to use the term limit of quantification (LOQ) instead of limit of determination	Also in list of endpoints

Confidential information has been removed by EPCO.

2. Mammalian toxicology (B.6)

No comments.

section 3 - Residues (B.7)

3. Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	Vol 1, 1.5.3 and Vol 3, B.3.2.3 and B.3.2.4, intended uses	NL: The use as seed treatment is not taken up in the tables	
(2)	Vol 3, B.7.2, Metabolism in domestic animals	NL: Contrasting to the plant studies, in animals no studies were done with the pyrimidine-labeled parent. Question: are all metabolites in animals covered by the other two labels?	
(3)	Vol 3, B.7.2.2 and B.7.9.2, Residues in poultry products	NL: It is not without doubt that residues in chicken products will be <0,01 mg/kg because extrapolation to lower doses is not by definition linear (e.g. a relatively high percentage might be excreted at high doses; metabolic pathways might be saturated at a 900X dose and therefore should not result in lower levels of metabolites at lower exposure levels per se). We agree that residues in poultry products will probably be low, but especially in liver it is doubtful to conclude that residues will be lower than 0,01 mg/kg.	
(4)	Vol 3, B.7.13, Justification of MRL's	NL: Adding the calculations (method I and II) for derivation of plant MRL's could help in interpreting the MRL proposals	

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section 3 - Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(5)	Vol 3, Chronic exposure	NL: No intake values were given for the WHO (Europe) diet.	

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section 4 - Environmental fate and behaviour (B.8)

4. Environmental fate and behaviour (B.8)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.8.3, PECs	NL: in the calculation of the cumulative concentration in soil and the accumulative potential it is calculated that a steady state of 0.018 mg fluoxastrobin/kg dry soil after three seasons following repeated annual use. Later in the text the tota; amount based on maximum PECs is calculated to be a concentration of 0.21 (1 year) plus 0.032 is 0.242 mg fluoxastrobin/kg dry soil. Is this correct shouldn't it be plus 0.018 = 0.228 mg/kg.	
(2)	Vol. 3, B.8.5.1, surface water	NL: it is not clear what calculation method has actually been used to derive the tables B.8.44 and B.8.45. Furthermore in the calculation of the PECsw for the metabolite the initial PEC of the parent is 3.17 μg/L coming form 2 applications with a drift value of 2.38%. This is a different calculation as was done for the parent itself (see table e.g. 8.44).	
(3)	Vol. 1, level 2, 2.5.3, fate and behaviour in water	NL: In the calculation of the PECsed it is not made clear that different spraydrift values lie beneath this result.	

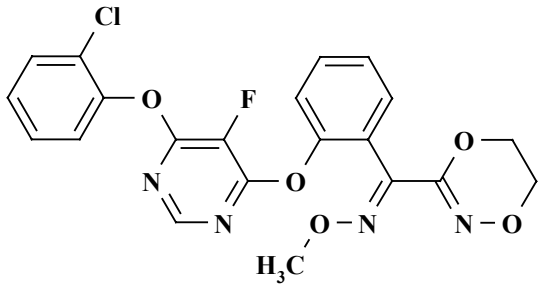
section 4 - Environmental fate and behaviour (B.8)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(4)	Vol. 1, level 2, list of endpoints	NL: PECsoil for M48 is only calculated for 258 days. The maximum % is already earlier in the degradation studies. Therefore we think the PEC soil should be calculated for all timepoints (to be used in the ecotox part as well). This hasn't been done throughout the total monograph	

5. Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	Vol. 1, list of end points, effects on terrestrial vertebrates	NL: Please report LC50 and NOEC also as daily dose (mg/ kg bw.d)	For risk assessments in line with the latest EU guidance (SANCO 4145/2000/EC, september 2002) LC50 and NOEC need to be expresssed as daily dose.
(2)	Vol. 1, list of end points, effects on terrestrial vertebrates	NL: NOEC for birds should be 461 ppm based on the study with Anas plathyrhinchos.	The lowest NOEC of 461 ppm used for the risk assessment should be reported as the relevant endpoint.
(3)	Vol. 1, list of end points, toxicity data for aquatic species	NL: Screening data for additional invertebrates are not mentioned.	The lowest relevant endpoint in the risk assessment is taken form the study with additional invertebrate species. As least the critical end point should be mentioned.
(4)	Vol. 1, list of end points, effects on other arthropod species	NL: Trigger for effects in extended laboratory test on Aphidius and Coccinella according to ESCORT 1 is 25% and not 30% as reported in the table.	
(5)	Vol. 3, B.9 Ecotoxicology, background information	NL: Seed treatment is not dealt with in the risk assessment for birds and mammals but might well be the worst case scenario.	On page 352 it is mentioned that “The use of a seed treatment followed by two foliar applications of HEC 5725 EC100 is assumed to represent the worst case scenario with respect to the environmental risk assessment”. Seed treatment is not reported under the intended uses and for instance not assessed in the the risk assessment for birds and mammals. This needs to be clarified.
(6)	Vol. 3, B.9.2.4	In table 9.17 % survival at day 28 is wrongly reported as % mortality at day 28.	

1. Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis (B.1-B.5)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, , B.1.1.5 CAS, EEC and CIPAC number Adjustments needed also in: Vol. 1, Level 1, 1.3.5; Vol. 1, Level 2, 2.1.1; Vol. 1, Appendix 1.2, List of end points	PSD has in agreement with BCS defined the E-isomer of Fluoxastrobin as active ingredient, therefore the correct CAS number is 361377-29-9. The Z-isomere should be declared as an impurity. The CIPAC number is 746.	
(2)	Vol. 3, , B.1.1.6 Molecular and structural formulae, molecular mass Adjustments needed also in: Vol. 1, Level 1, 1.3.6; Vol. 1, Appendix 1.2, List of end points	Molecular formula is incorrect, reflecting the E- and Z-isomer ! Correct structural formula is as follows: 	
(3)	Vol. 3, , B.2.15 Physical/chemical properties	Shelf life study was submitted to the Rapporteur in August 2003. ~~The respective reports MO-03-007195 + MO-03-007196 are attached~~.	

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No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(4)	Vol. 3, , B.5.2 Method of analysis Validation	Table B.5.2 Precision – repeatability (CV)%: Seite: 2 [0]Statistically, the values we cite in the reports were not calculated as CV (coefficient of variation) but at standard deviation (SD), or relative standard deviation (RSD) Fortification levels: The assignment of the fortification levels for the isomers for this method is not consistent with the way the fortification levels were assigned for the other methods and for the wheat matrices for this methods (see next page). To achieve consistency, the values would have to be changed as noted. Leaving the values as they are (i.e. all three values for fluoxastrobin and the 2 isomers at the same level) is not necessarily wrong, it should only be kept in mind that in this case the give fortification level refers always to fluoxastrobin and not to the isomers (i.e. we did not fortify 0.02 mg/kg Z-isomer but 0.002.	

2. Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.6.6.1, Multi-generation study in rats with fluoxastrobin	The applicant proposed a higher NOAEL (1,000 ppm) for developmental effect. Justification: Due to the size of the thymus in a 21-day-old pup, there is a significant animal-to animal variation in weight, not only to normal variation, but also due to the excision and trimming of such a tiny organ. The thymic weights in the control animal ranged from 0.029 – 0.340 g in the male, and 0.092 – 0.379 g in the female. Moreover, the standard guideline procedure in place during the execution of the study was to necropsy only one male and one females per litter (if one of each batch was available), Inadvertently contribution additional variability due to random selection based on sex and not body weight. In addition to clarify the situation the histopathologyical evaluation of the thymus will be performed; results will be available April 2004.	

section 2 - Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(2)	Vol 1, Appendix 1.2 List of end points Adsorption, distribution, excretion and metabolism in animals, page 62	Under item *Toxicologically significant compounds* delete and metabolites. The parent compound only is toxicologically significant as none of the non-common metabolites in crops and animal tissues are considered to be of sufficient toxicological concern to be of relevance for consumer risk assessment under the proposed condition of use. For metabolites M40 and M48 identified in environmental fate studies applies the same, see also Vol 3, B 6.8.	

section 3 - Residues (B.7)

3. Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol . 3, B 7. Vol. 1, Level 1, 1.5.3 Vol. 1, Level 2, 2.4 Residue data	The use of foliar spray of fluoxastrobin support the uses in wheat, rye in general as well as to triticale. Extrapolation from wheat to rye and triticale is aimed at. Triticale is not mentioned in Vol. 1, Level 1, 1.5.3 and Vol. 1, Level 2, 2.4. Furthermore extrapolation from barley to oat is aimed at.	
(2)	Vol . 3, B 7.6.1 Cereal crops	Page 265 in the tables typing error: application rate per treatment 300 l/ha water instead of 3000.	
(3)	Vol . 3, B 7.6.2.2 Barley	In the part Southern Europe: Typing error: should be barley instead of wheat.	
(4)	Vol . 3, B 7.9. Domestic animal feeding studies	Compiling the residues of fluoxastrobin (as sum of parent and ist phenoxy-hydroxypyrimidine metabolite expressed as parent) in milk and tissues it is not clear how the single values have been calculated if residues were less than LOQ. In the dossier calculation was done in a different way. Where the residue value is less than the LOQ, the value of the LOQ was used to calculate the sum of	

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section 3 - Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		parent compound + metabolite expressed in parent compound equivalents. In consequence this leads to lower MRL proposals than in the dossier in three cases for animal products. Commodity Proposed MRL (dossier) mg/kg proposed MRL (DAR) mg/kg Milk 0.05 0.01 Meat 0.05 0.02 Liver 0.1 0.05 As to our knowledge the common procedure is summing up the LOQs in case one or more single values for the isomers and metabolite are less than the LOQ we have to ensure that we do not run into problems with enforcement, especially with PSDs MRL proposal for milk (0.01 mg/kg). The LOQ of the enforcement method provided is	

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section 3 - Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		0.01 mg/kg for the sum of HEC 5725 E-Isomer and HEC 5725 Z-Isomer and for the relevant metabolite HEC 7154, respectively. This leads to a total of minimum 0.02 mg/kg. To avoid exceeding of MRLs, due to different calculation modi, we propose to stay with the proposed MRL's.	

4. Environmental fate and behaviour (B.8)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.8.1.3.2 Field accumulation Adjustments needed also in: Vol. 1, Appendix 1.2, List of end points	Soil accumulation testing is not necessary since DT90 field values of fluoxastrobin (mean) are less than one year.	
(2)	Vol. 3, B.8.4.3 Ready biodegradability Adjustments needed also in: Vol. 1, Appendix 1.2, List of end points	A study on ready biodegradability of fluoxastrobin was not performed. However, this requirement is covered by the water-sediment study.	

5. Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	Vol. 3, B. 9.2.1, Aute / Chronic aquatic toxicity Tables B 9.12 Adjustments needed also in: Vol. 1, Level 2, 2.6.2; Vol. 1, Appendix 1.2, List of end points	In the table (B 9.12) values derive the non-GLP study. Since the GLP study is available (06/2003), these values has to be inserted. ~~GLP study 200306_ALT.RW.2003.1_MO-03-007803.pdf~~ attached as well as table 1 in document <<03 Fluoxastrobin comments NOT ecotox B9.doc>>	
(2)	Vol. 3, B.9.2.4.1, Chronic toxicity of fluoxastrobin to fish and aquatic invertebrates	Table 9.17, second column heading: % **survival** at day 28 insead of % mortality.	
(3)	Vol. 3, B.9.2..4.1, Chronic toxicity of fluoxastrobin to fish and aquatic invertebrates Adjustments needed also in: Vol. 1, Level 2, 2.6.2; Vol. 1, Appendix 1.2, List of end points	Additional higher tier study with *Gammarus pulex* is available ~~and attached 200310_P1MG_ECT Final_MO-03-013843.pdf .~~	

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section 5 - Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(4)	Vol. 3, B.9.2.5.1, Acute risk to aquatic life from spray drift	Acute risk assessment as well as TER's in table B 9.22 has to be carried out with values of the GPL study and not with those of the non-GLPstudy, see also comments under point 1 and table 2 in document<<03 Fluoxastrobin comments NOT ecotox B9.doc>>	
(5)	Vol. 3, B.9.2.5.2, Chronic risk to aquatic life from spray drift	*Gammarus pulex* study has to be considered in the chronic risk assessment, see attached statement <<03 Fluoxastrobin comments NOT risk assessment aquatic-invertebrates.pdf>>	
(6)	Vol. 3, B.9.2.5.7, Aquatic risk assessment conclusion and labelling	Change conclusion based on new information provided, see also comment point (1) and (5).	
(7)	Vol. 3, B. 9.5.4.3, Proposed product labelling and risk mitigation	According to our opinion no additional risk mitigation necessary, see statement <<03 Fluoxastrobin statement NOT buffer zone.pdf>>	
(8)	Vol. 3, B.9.6.2, Risk to earthworms	3rd and last para : log Kow of metabolites is **< 2** and not >2 see also dossier part 10.1.4.2. Therefore in Table B.9.36 the 14 day LC50 for the metabolite HEC 5725-deschlorophenyl is >1000 and not >500 mg/kg dry soil.	

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section 5 - Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(9)	Vol. 3, B.9.7.5, Risk assessment to evaluate impact of HEC 5725 EC 100 on macro-organisms that contribute to organic matter breakdown	4th and 6th para : log Kow of metabolites is **< 2** and not >2 see also dossier part 10.1.4.2. Therefore in Table B.9.41 the NOEC *Folsomia* for the metabolite HEC 5725-deschlorophenyl is 100 and not 50 mg/kg dry soil.	

section 1 - Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis (B.1-B.5)

1. Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis (B.1-B.5)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B 8.5.3.1,mobility of metabolite M48	DK: We have noted that one metabolite, M48, is problematic due to leaching	
(2)	Vol. 3, e.g. acute toxicity Table 9.12, chronic toxicity p. 369, aquatic risk assessment p. 374 + 377	DK: Comment on the inclusion of a salt water species (Americamysis bahia). We note that this species and the test results have been considered valid. Therefore we think that the results should be included in the endpoint list – they seem to be missing.	
(3)	Endpoint list, Soil adsorption/desorption	DK: Concerning the leaching of M48 we suggest to also state in the end point list that M48 exceeded 0.1 μg/l in 8 of the 9 FOCUS scenarios rather than just giving the interval.	
(4)	Endpoint list, Toxicity data for aquatic species	DK: The results from testing Americamysis bahia should be included	

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section 2 – Mammalian toxicology (B.6)

2. Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
		DK: no comment	

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section 3 – Residues (B.7)

3. Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
		DK: no comment	

section 4 – Environmental fate and behaviour (B.8)

4. Environmental fate and behaviour (B.8)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		DK: no comment	

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5. Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
		DK: no comment	

2. Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol.1, level 2, 2.3.1"Need for further toxicology information"	SE: We agree with the comment from DE (1 and 2) that the genotoxic properties of the impurities from the technical active substance have to be investigated before an Annex 1 inclusion.	
(2)	Vol.3, B.6.6.1, Multigeneration study in rat	SE: In general, several effects on the endocrine organs (such as uterus, pituitary, prostate, adrenals, male reproduction tissue, and thyroid) were observed in different species and studies after fluoxastrobin administration. At the same time, we considerer that the effects found in the multigeneration study were not describe with sufficiently transparency in the DAR.	Some of the points which need clarification: In the adults animals, was there any another effects than reduce body weight gain in males at 10000ppm (15%)? The total number of pups found dead in the highest dose was presented as nr/dose group. How many dams were involved? And how many pups were found in the control group? Was there any evidence in the multigeneration study which shows that the effects found in the thymus, the ovaries and uterus of the pups should be correlated to the effects in the dams?
(3)	Vol.3, B.6.6.2, Developmental toxicity in rat	SE: We don't agree with the conclusion of the RMS regarding the incomplete ossification of the forelimbs in rats. We considered that the NOAEL for development should be 100 mg kg^{-1} bw day^{-1} based on the skeletal findings in rats at 300 and 1000 mg kg^{-1} bw day^{-1}	The increases in abnormal skeletal in the rat were statistically significant in the two highest doses and the number of incidents was also higher than in the historical control.

1. Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis (B.1-B.5)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol 1. General.	EFSA: Identity of the active substance should be clarified in Vol 1. It is not clear whether Z-isomer should be considered also active component of Fluoxastrobin or and impurity. Also purity should be clarified.	Vol 1.3.3 IUPAC and CA name given only for the E isomer. Vol 1.3.5-1.3.6 CAS number and structural formula given for both isomers. Furthermore in Residues (Vol 1 2.4) parent is referred as sum of isomers whereas in Fate & Behaviour Vol 1. 2.5.2 it seems to be assumed that Z-isomer is mainly a transformation product. However, for residue definition in the environment it is not clear if Z isomer is included under “active substance fluoxastrobin”. It should be stated whether minimum purity is based on E isomer alone or on the sum of isomers. Second sentence in Vol 1. 2.1.1 is confusing since it may lead to believe that minimum purity is 980 g / Kg (based on E-isomer) whereas in other parts of the DAR it is stated that minimum purity is 910 g / Kg.
(2)	Vol 1. General.	EFSA: GAP needs to be clarified. A seed use previous to the foliar one is referred all thorough the DAR but is not collected in the Summary of intended uses.	
(3)	B1 (Vol 1. Level 4.2.1)	EFSA: Data requirement for revised technical specifications supported by 5 batch analysis when full scale manufacturing is in progress is confirmed.	

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section 1 – Physical/Chemical Properties; Details of Uses and Further Information; Methods of Analysis (B.1-B.5)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(4)	B1 (Vol 1. Level 4.2.1)	EFSA: Data requirement for validation of methods employed on the analysis of 5 representative batches when full scale manufacturing is in progress will be confirmed if different to the methods already reported.	EFSA: This data requirement should be under Level 4.2.5 if confirmed.
(5)	B2. General	EFSA: Acceptability and GLP of the studies should be stated in the DAR.	
(6)	B2.2.2.15 (IIIA 2.7) (Vol 1. Level 4.2.2)	EFSA: Data requirement for stability after two year storage is confirmed.	
(7)	B2.2.17 (IIIA 2.8) (Vol 1. Level 4.2.2)	EFSA: Data requirement for the antifoam agent effectiveness is confirmed.	
(8)	B2. References.	EFSA: References should be found at the end of the chapter.	
(9)	B3. References.	EFSA: References should be found at the end of the chapter.	
(10)	B5. General.	EFSA: Linearity is not reported in the DAR for any of the analytical methods.	
(11)	B.5.1.1 / B.5.1.3	EFSA: Method for the analysis of pure active substance in technical material and plant protection product can not be confidential.	

2. Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol 1. General. End Points table. Toxicologically significant compounds (animal, plants and environment).	EFSA: It should be clarified which metabolites are considered toxicologically relevant.	
(2)	Vol 3. Annex B.6 B.6.2.7	EFSA: fully support the need to perform the skin sensitization assay with batches of similar quality than the final production ones	
(3)	Vol 3. Annex B.6 B.6.3.4	EFSA: in the 4 weeks dermal study in rats, fluoxastrobin was moistened with water ; this is not representative of the intended final formulation	
(4)	Vol 3. Annex B.6 B.6.4	EFSA: Most of the test were performed with purity grade higher than the one intended for the final formulation. A special attention should be paid to the fact that not only the purity of the test agent must be taken into account for the expression of genotoxic and/or mutagenic potential ; the nature and levels of impurities are also of relevance for these studies.	

section 2 - Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(5)	Vol 3. Annex B.6 B.6.4.1 P 130	EFSA : The following phrasing is proposed for the cecond part of the conclusions "however it should be noted that although this study complied with OECD guidelines, this type of study with CHO cells is now considered by some bodies to be insufficiently sensitive (predominantly on statistical grounds) and the mouse lymphoma assay is preferred, see Committee on Mutagenicity (2000)." "however it should be noted that although this study complied with OECD guidelines, the gene mutation assay at the thymidine kinase locus (TK) in L5178Y mouse lymphoma cells is considered by some bodies to be a preferable choice (predominantly on statistical grounds) than the HPRT gene mutation assay on either chinese hamster ovary (CHO) or V79 chinese hamster lung cells, see Committee on Mutagenicity (2000)."	

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section 2 - Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(6)	Vol 3. Annex B.6 B.6.4.1 P 132	EFSA : The following phrasing is proposed for the cecond part of the conclusions "however it should be noted that although this study complied with OECD guidelines, this type of study with CHO cells is now considered by some bodies to be insufficiently sensitive (predominantly on statistical grounds) and the mouse lymphoma assay is preferred, see Committee on Mutagenicity (2000)." "however it should be noted that although this study complied with OECD guidelines, the gene mutation assay at the thymidine kinase locus (TK) in L5178Y mouse lymphoma cells is considered by some bodies to be a preferable choice (predominantly on statistical grounds) than the HPRT gene mutation assay on either chinese hamster ovary (CHO) or V79 chinese hamster lung cells, see Committee on Mutagenicity (2000)."	

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section 2 - Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(7)	Vol 3. Annex B.6 B.6.4.3	EFSA : As far as the batches used for genotoxicity/mutagenicity testing are of different purities than the final full production batch, the lack of genotoxic and/or mutagenic potential has to be confirm by robust scientific testing ; the HPRT assays does not appear sufficient in this way. EFSA strongly recommend to repeat testing - at the gene level – in a first instance, by doing gene mutation assays on both bacteria and on mammalian cells (L5178Y mouse lymphoma cells at the thymidine kinase locus). Taking into account the results obtained with the final full production batch, further information by applying additional genotoxicity tests may be necessary to confirm the lack of genotoxic potential of impurities.	

section 4 - Environmental fate and behaviour (B.8)

3. Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, 2.4.1 Definition of the residue relevant to MRLs Vol. 1 App. 1.2, Listing of endpoints-Animal residue definition for monitoring	EFSA: Animal residue definition for monitoring in Listing of endpoints is in contradiction to the given residue definition for monitoring in the DAR RMS to verify and to revise	
(2)	Vol.1 App. 1.2, Listing of endpoints-proposed MRLs Vol. 3, B.7.13 proposed MRLs and justification for the acceptability of those residues	EFSA: MRL proposals for animal products have to be revised depending from the decision on animal residue definition for monitoring	proposed MRLs should consider the measured residues as well as in case of non-detection the efficiency of the analytical method with regard to the given LOQ for each, parent and metabolite M55

General comment concerning Methods of Analysis

	Vol.1 App. 1.2, Listing of endpoints- Methods of Analysis	EFSA: the LOQ should be reported clearly for each single compound in relation to the analysed matrices RMS to revise the list of endpoints	Depending from the matrix analytical methods are validated for parent compounds and several metabolites. Reporting of a general range is not sufficient.

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4. Environmental fate and behaviour (B.8)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol3. B.8.1 / B.8.5.3 and Vol 1. Level 4.2.8.	EFSA: Need for a data requirement at MS level to assess anaerobic water / sediment metabolite M40 for ground water contamination should be considered.	Anaerobic water / sediment study was submitted as a surrogate of the anaerobic soil degradation study. M40 is a major metabolite in this study (> 10 % and maximum not reached at the end of the study) and therefore it should be considered to be a major metabolite in soil under anaerobic degradation. According Doc. SANCO/221/2000-rev 10 metabolites found in soil studies under normal conditions of use should be assessed for potential ground water contamination. When dealing with authorizations where anaerobic conditions are expected to be relevant this assessment should be performed.
(2)	B.8.4.2	EFSA: Need to assess aqueous photolysis metabolite M36 (up to 23.6 % at the end of the study) for ecotoxicological and/or toxicological relevance should be considered. (Note this metabolite is not common to mammalian metabolism).	
(3)	B.8.4.2	EFSA: Estimated half-life of M36 (oxazepine) metabolite in aqueous photolysis study is not reliable since there are no data points after the maximum is reached.	
(4)	B.8.9.	EFSA: Z isomer of Fluoxastrobin should be considered for inclusion in soil residue definition on basis of soil photolysis study.	
(5)	B.8	EFSA: References should be at the end of the chapter.	

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5. Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, List of endpoints and Vol. 3, B.9.1.3.3, long term risk to birds	EFSA : The long term risk assessment for birds in the DAR and the list of endpoints was each time based on a different endpoint. Please verify and justify the choice of endpoint made.	
(2)	Vol. 1, List of endpoints, toxicity data for aquatic species	EFSA : TER value from the most critical endpoint in the DAR should be mentioned as well in the list of endpoints.	
(3)	Vol. 1, List of endpoints, toxicity data for aquatic species	EFSA : In the list of endpoints an EbC50 > 115 mg metabolite/L is mentioned for the acute toxicity of HEC 5725-carboxylic acid for daphnia while it seems in the DAR that this endpoint equals 115 mg metabolite/L.	
(4)	Vol. 3, B.9.2.5, Table B.9.22	EFSA : Further information on the need at member state level of a repetition of the non-GLP study by Wijngaarden (2003) to be able to reduce the bufferzone, is considered necessary.	It is noted that endpoints of a non-GLP study were used in the risk assessment as this was the most sensitive endpoint. Furthermore it is noted that the same non-GLP study was used to reduce the Annex VI trigger from 100 to 10. Nevertheless the acute risk assessment based on GLP or on non-GLP data comes to the same conclusion.
(5)	Vol. 3, B.9.2.5.2, p. 376	EFSA : How was the initial PEC calculated for sediment dwelling organisms.	
(6)	Vol. 3, B.9.2.5.2	EFSA : In order to be able to confirm the outcome of the chronic aquatic risk assessment the additional higher tier study with *Gammarus pulex*, by liebig M. (2003) should be evaluated by the rapporteur.	

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section 5 - Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(7)	Vol. 1, List of endpoints, toxicity data for bees	EFSA : In the list of endpoints an oral HQ < 7.5 is mentioned for the product while it seems that in the DAR this HQ equals 7.5.	
(8)	Vol. 1, List of endpoints, effects on other arthropod species	EFSA : Results for *Chrysoperla carnea* are not mentioned in the list of endpoints.	
(9)	Vol. 3, B.9.4.3, Risk to bees	EFSA : it is noted that the risk to bees was calculated for one application only.	
(10)	Vol. 3, B.9.5.4.2, p. 391	EFSA : It is noted that a spray interval of 14 days is taken into account to calculate the risk for NTA while no precise interval is given in the summary of intended uses.	
(11)	Vol. 3, B.9.5.4, Risk assessment for non-target arthropods	EFSA : It is noted that acceptable risk is not proven in a study for 2 crop specific species *Chrysoperla carnea* and *Coccinella bileneata*. Basing the acceptability of the risk on the short persistence of the parent in a semi-field study with *A. rhopalosiphi* and the residue decline on foliage is rather limited.	
(12)	Vol. 1, List of endpoints, effects on earthworms and other soil macro-organisms	EFSA : The TER-values mentioned in the list of endpoints do not correspond to the TER values for earthworms or other soil macro-organisms mentioned in the DAR.	

section 5 - Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(14)	Vol. 3, B.9.7.2, collembola	EFSA : No statistically significant difference in reproduction was observed after exposure of *F. candida* to HEC 5725-deschlorophenyl consequently the NOEC was set at the highest tested dose. Although not statistically significant the observed 30% effect on reproduction at the highest tested dose can not be ignored.	
(15)	Vol. 1, List of endpoints, results of litterbag study	EFSA : Please mention the tested dose in the litter bag study as well as in the list of endpoints.	