PEER REVIEW REPORT ON **CYFLUFENAMID** 08 02 2008

TABLE OF CONTENTS

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)	Vol. 1, General	EFSA: RMS should consider to use the current harmonised version of the list of end points.	RMS: Due to resource limitations we have not re-formatted the endpoints at this time to the Sept 05 guidance. We undertake to do this in time for the PraPer expert meetings. Open point	Open point: RMS should consider using the current harmonised version of the list of end points. See also 0(3)
0(2)	Vol 3, B.2, physical and chemical properties	NL: Please state for every study whether GLP compliance is met.	RMS: All the studies requiring to be to GLP were unless stated. Addressed	Addressed: The rapportuer has confirmed that GLP requirements have been met.
0(3)	Vol. 1, List of endpoints, section ecotoxicology, General	EFSA: It is noted that not the latest template for the list of endpoints was used (See EPCO Manual E4 rev.4 of September 2005).	RMS: Due to resource limitations we have not re-formatted the endpoints at this time to the Sept 05 guidance. We undertake to do this in time for the PraPer expert meetings. Open point	See open point in comment 0(1)

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. 4, C.1.2 detailed specification of the active substance, p. 5	EFSA: Taken the given batch analyses into account it seems that a minimum purity of 980 g/kg would be reliable. Are other data available (e.g. QC data) to support the value of 970 g/kg?	RMS: 970 g/kg was considered acceptable as although the minimum in the five batches was 988 g/kg, the five batches only represent a small part of the overall production (no further QC data on other batches were requested). Addressed	Data requirement: The applicant should justify the minimum purity of the active substance given that the batch data suggest that 980 g/kg would be reliable. It should be noted that the applicant has stated that QC data has been sent to the rapporteur on 6 June 2007.
1(2)	Vol. 4, C.1.3 detailed specification of the preparation, p. 8	EFSA: The content of pure cyflufenamid should be given as required according to Directive 94/37/EC.	RMS: The content is 50 g/l pure cyflufenamid (50.5 g/l technical based on mean purity of 99%). Addressed	Addressed: Rapporteur to consider in a revised DAR or corrigendum. See also 1(10)
1(3)	Vol. 1, LOE CIPAC No., pg 49	AT: 759 should be added.	RMS: Agreed. Addressed	Open point The CIPAC number 759 should appear in the list of end points. See also 1(4).
1(4)	Vol 1, 1.3.5, CIPAC number	NL: CIPAC number is 759 for cyflufenamid (source: www.cipac.org).	RMS: Agreed. Addressed.	See open point in comment 1(3)
1(5)	Vol 4, C.1.2, 5 batch analysis (pg 5)	NL: For all impurities, except PAA and 149-E the LOQ of the analytical method does not allow determination of impurities at the reported concentrations. For 149-O-B it might be necessary to include this impurity in the specification. The measurements with values below the LOQ	RMS: Refer to 1(36).	Open point: The method of analysis with regard too the LOQ should be discussed in a meeting of experts. See also 1(36). The applicant has ststed that a report will be available September 2007.

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)
		of the method should be mentioned as < LOQ.		

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(6)	Vol. 1, List of end points, active substance, p. 49	EFSA: It seems that an entry in the box is missing.	RMS: The ISO common name (ISO accepted) is 'cyflufenamid'. The Endpoints have been updated. Addressed	Addressed: The endpoints have been amended.
1(7)	Vol. 1, List of end points, UV/absorption, p. 50 in relation to volume 3.	EFSA: The values for molar absorption coefficient should be given. Furthermore, the pH value should be given.	RMS: The pH was not stated in the study, however the endpoints have been updated with the molar absorption coefficients	Addressed: The endpoints have been amended
1(8)	Vol. 3, B.2.4 References relied on, p. 15 onwards	EFSA: The studies on the metabolites (e.g. solubility in water or partition coefficient) should be removed from the references relied, because these studies are not required according to Directive 94/37/EC.	RMS: Agree. The references relied on list will be updated with these studies removed. Open point	Open point: Rapporteur to update the list of references relied on to remove the references to solubility and partition co-efficient for the metabolites.
1(9)	Vol. 3, B.2.1.10 UV spectra acidic medium, pg 4	AT: The value for ε at 361 nm should be inserted at least.	RMS: The molar coefficients are as follows; Neutral - λ_{max} 207 nm ($\varepsilon = 2.08 \times 10^4$ l mol^{-1} cm^{-1}) 238 nm ($\varepsilon = 1.29 \times 10^4$ l mol^{-1} cm^{-1}) Acidic - λ_{max} 207 nm ($\varepsilon = 2.11 \times 10^4$ l mol^{-1} cm^{-1}) 238 nm ($\varepsilon = 1.32 \times 10^4$ l mol^{-1} cm^{-1}) 361nm ($\varepsilon = 1.78 \times 10^2$ l mol^{-1} cm^{-1})	Open point: UV spectra. The rapporteur to add all the molar coefficients to the list of end points.

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)
			Basic - λ_{max}220 nm (ε= 1.30 x 10^4 l mol^{-1} cm^{-1}) 240 nm (ε= 1.18 x 10^4 l mol^{-1} cm^{-1}) Addressed	

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(10)	Vol. 1, 1.4.5 Composition of the preparation, p. 6 in relation to volume 4	EFSA: The content of the cyflufenamid in the preparation needs to be clarified. The given values do not fit together (e.g. the amount of technical material is lower than for the pure substance) and the given typical purity is lower that the specified minimum purity.	RMS: Agreed. The correct details are:– "Pure active substance: 50 g/l of cyflufenamid (NF-149) Technical active substance: 50.5 g/l (technical) (at a typical purity of the technical a.s. of 99%)". The technical active substance was previously 54 g/l, however due to the change in the nominal purity of the technical material this has been revised to 50.5 g/l. Addressed	See comment 1(2).

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(11)	Vol. 3, B.2.2.14 storage stability, p. 12	EFSA: The need for the proposed labelling is unclear, since the requirement of the FAO/WHO manual is fulfilled. In addition to this, MT 39.3, the recommended method according to Directive 94/37/EC, is designed to determine any kind of separation and nothing more.	RMS: The limit for rinsed residue in the pourability test (CIPAC MT 148) is 0.25% as stated in the document, the result obtained after 2 years storage was 0.4% and therefore the reason the labelling was required. Due to the limited data the test gives i.e. separation only (no data on retention of active substance and emulsion stability) and the formulation being water based a precautionary phrase was felt appropriate. Addressed	Addressed: Labelling is a Member State issue.
1(12)	Vol. 3, B.2.2.14 low temperature stability, pg 12	AT: The precaution on the label should not be supported by missing data but by results of studies. Data concerning low temperature stability are requested.	RMS: The 'Protect from Frost' recommendation is a well established precautionary phrase where either only limited or no data are available. Addressed	Addressed: The cold temperature stability study is available in the DAR.
1(13)	Vol 3, B.2.2.17, persistence of foam, pg 13	NL: At what concentration was the test performed?	RMS: 0.5%v/v (which is identical to the proposed rate of use). Addressed	Addressed: There was only 7 ml after one minute it is not an issue.

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(14)	Vol 3, B.2.2.26, emulsifiability, pg 14	NL: At what concentration was the test performed? What was the situation at 4 hours? In what type of water was the test performed and at what temperature?	RMS: 1 and 5%. The 100% result was after 4 hours (1% - 99% and 5% - 103%), the result in brackets was for CIPAC MT 36 for concentrations of 0.1 and 0.5%. CIPAC water A and D Addressed	Addressed: It is clear that a stable emulsion is formed.
1(15)	Vol 3, B.2.2.13, relative density, pg 11	NL: This is not a relative density. At what temperature was the density determined?	RMS: Agree. Temperature 20°C. Addressed	Addressed: Rapporteur to consider in a revised DAR or corrigendum.
1(16)	Vol 3, B.2.2.20, dilution stability, pg 13	NL: Please mention this determination is not a requirement or mention at what concentration the test was performed (0.25% required).	RMS: Agree, test is not required for EW formulations. Addressed	Addressed: Dilution stability is not a requirement for EW formulations.

Further information (B.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)
1(17)	Vol. 3, B.3 Data on application and further information, in relation to references relied on	EFSA: It seems that not all of the studies mentioned in the chapter references relied on are quoted in chapter 3 (e.g. Anon, 2002).	RMS: The references will be deleted from the updated references relied on list accordingly. Open point	Open point: Rapporteur to update the references relied on.

Further information (B.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)
1(18)	Vol. 3, P27, B.3.5.3 Re-entry period, necessary waiting period or other precautions to protect man, livestock and the environment (IIIA 4.3)	NOT: There is no information on the re-entry periods below the heading B.3.5.3.	RMS: Agree. For re-entry/waiting periods see below: Pre-harvest intervals: Wheat, rye and triticale – PHI 42-77 days Barley: 49-70 days (Northern Europe), 22-56 days (Southern Europe) Re-entry period for livestock to pasture: NF-149 is not intended for use in areas where livestock animals may be grazed. Therefore, no re-entry period is proposed. Re-entry period for man to treated areas: NF-149 is intended for use on winter cereals and re-entry into such treated fields is generally not necessary. No re-entry period is proposed for European product labels. Withholding period for animal feedstuffs: Due to the time between last treatment and harvest, as defined by the GAP, it is not necessary to set a withholding period for use of treated plants as animal feedingstuffs. The withholding period is covered by the vegetation period of the crop. Waiting period before handling treated products: Allow crops to dry after spraying before handling. Waiting period before succeeding crops: No restrictions are proposed for the choice of following crop grown in rotation after winter cereals.	Addressed: Rapporteur to consider in a revised DAR and corrigendum.

Further information (B.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)
			In the event of crop failure, a 30-day withholding period is recommended before a following crop is sown. There is also no requirement for a waiting or withholding period after winter cereals.	

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(19)	Vol. 3, B.5.2 Analytical methods (residue) for treated plants…, p. 37	EFSA: The applicability of a multi-residue-method needs to be addressed.	RMS: The method submitted involves the general principles of a multi-residue method as described in SANCO/825/00. The only significant difference is that the submitted method uses methanol/acetone as an extraction solvent rather than pure acetone. Cyflufenamid, which is the only component of the residue definition in plants, has equally high solubility in both acetone and methanol. The RMS therefore considers that the method proposed is compatible with a multi residue method and further data are not required. Addressed.	Addressed: It is likely that this compound will fit in existing multi-residue methods.
1(20)	Vol. 3, B.5.3.3 residues in water, p. 38	EFSA: It should be noted that as long as no residue definition for air is proposed, a final assessment of the analytical method is not possible.	RMS: Agree. Addressed	Open point: A final assessment of the air method is not possible until a residue definition is set.

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(21)	Vol. 4, C.1.4.1 Analytical methods of impurities, p. 9 – 11 in relation to the references relied on	EFSA: It should be noted that according to Directive 96/46/EC only methods for the determination of significant and/or relevant impurities must be provided. Therefore, the RMS should consider to amend the references relied on to indicate that these methods are not necessary and or additional data.	RMS: The RMS agrees that methods are only required for the determination of significant/relevant impurities. The methods for the determination of [redacted] and [redacted] were used in the determination of the purity of the purified active substance and were not relied on to determine the analytical profile of batches. The list of references will be updated accordingly. The study Unemoto, T, 2000, will be deleted from the updated references relied on list. Open point	Open point: Rapporteur to amend the list of references relied on to remove the reference to impurity methods that are not required.
1(22)	Vol. 1, LOE analytical methods	AT: The LOQs should be added.	RMS: Endpoints have been updated. Addressed.	Addressed: The end points have been amended.
1(23)	Vol. 3, B.5.1.1, B.5.1.3 and B.5.2.1 Vol. 4, C.1.4.1 analytical methods in general	AT: More information concerning linearity is required (levels, correlation coefficients).	RMS: The linearity was demonstrated over appropriate ranges for all analytes. The correlation coefficients were >0.99 in all cases. Addressed.	Addressed: The rapporteur has confirmed that the methods are linear in an appropriate range.
1(24)	Vol. 3, B.5.3.2 analytical methods water, pg 37	AT: A linearity range of 0.01 – 0.2 µg/mL cannot cover fortification levels of 0.1 to 10.0 µg/kg (the unit in the table header should be changed from mg/kg to µg/kg).	RMS: Based on the dilution factor of the method, levels of 0.01 to 0.2 µg/l in the final extracts equate to residue levels in the initial samples of 0.05 to 1.0 µg/l (0.05 to 1.0 µg/kg). This covers the lower end of the validated range. Higher residues were diluted into the calibration range. Addressed.	Addressed: The higher levels are diluted in to the linear range. Rapporteur to consider amending the table header for the water method changing mg/kg to µg/kg in a revised DAR or corrigendum.
1(25)	Vol. 3, B.5.3.3 analytical methods	AT: A linearity range of 0.05 – 1.0 µg/mL	RMS: Based on the dilution factor of the method, levels of 0.05 to 1.0 µg/l in the final extracts	Addressed:

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)
	air, pg 38	cannot cover fortification levels of 1 to 100 µg/m^3.	equate to residue levels in the initial samples of 0.43 to 8.7 µg/m^3. This covers the lower end of the calibrated range. Higher residues were diluted into the calibration range. Addressed.	The higher levels are diluted in to the linear range.
1(26)	Vol 1, LOEP, analytical methods for food/feed of plant origin	NL: Please mention LOQ's, validated analytes and matrices, confirmatory methods and ILV.	RMS: Endpoints have been updated. Addressed.	Open point: For the residue methods the analyte should be mentioned in the LOEP. See also 1(27).
1(27)	Vol 1, LOEP, analytical methods for soil, water and air	NL: Please mention LOQ's, confirmatory methods, analytes and matrices (surface water, drinking water).	RMS: Endpoints have been updated. Addressed.	See comment in open point 1(26).
1(28)	Vol 3, table B.5.1, LOQ pg 36	NL: The footnote makes no sense: there is no LOQ mentioned in the table?	RMS: This is an error. The footnote applied to the LOQs for the impurities in the technical meeting and should have been removed when the validation data for the impurities were moved into Volume 4. An LOQ for the active substance in the technical material is not required. Addressed.	Addressed: Rapproteur to consider in a revised DAR or corrigendum. See also 1(30)
1(29)	Vol 3, table B.5.2, linearity, pg 36	NL: Does 0.12 mg/ml – 0.67 mg/ml correspond to 35 to 200% of the declared contents of active substance? The mentioned data seem incomplete or incorrect: the nominal concentration is 5%w/w which is roughly equal to 50mg/ml. The lack of a thorough description of the method is not acceptable.	RMS: The units in the table are incorrect. Based on the dilution factor of the method, levels of 0.125 to 0.67 mg/ml in the final extracts equate to levels in the initial samples of 1.8 to 10.0 % w/w which is ~35 to 200 % of the nominal concentration of 5 %w/w. Addressed.	Addressed: Rapporteur to consider in a revised DAR or corrigendum.

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(30)	Vol 3, table B.5.1, LOQ pg 36	NL: No LOQ is mentioned in the table. What does the footnote refer to?	RMS: Refer to comment 1 (28).	See comment 1(28).
1(31)	Vol 3, B.5.1.1, technical active substance, pg 35	NL: The method should be more clearly described, including dilution ratios. With the mentioned data it is impossible to conclude linearity was correctly demonstrated.	RMS: The RMS considers that the level of detail reported is sufficient. Table B.5.1 reports that the linearity was demonstrated over an appropriate range, equivalent to 50-150 %w/w. The RMS has concluded in Section B.5.5. that the method validation is acceptable. Addressed.	Addressed: This can be accepted for the moment guidance on reporting detail is currently under discussion. See also 1(35).
1(32)	Vol 3, table B.5.3., analytical method (residue) for food/feed of plant origin, pg 39	NL: The method is not acceptable. Batch 1 displays a very high standard deviation (RSD > 20%) and accuracy is below acceptable limits for various fortification levels.	RMS: In Section B.5.5. the RMS notes that the ILV data were initially unacceptable (high precision and/or low recovery values). It is reported that following communication with the study monitor and the developers of the method, minor modifications were made to the method and acceptable data were generated. The modifications involved reducing the batch size and storing only the cyclohexane/ethyl acetate extracts overnight. The RMS considers that these are minor changes to the method and do not affect the validity of the method as a post-registration monitoring and enforcement method. Addressed.	Open point: From the comment made by the rapporteur in column 3 of the reporting table it would appear that there was some communication between the primary lab and the lab that conducted the ILV such that initially the method did not work. This is not correct procedure and this issue should be discussed in a meeting of experts. The applicant has stated that a justification will be provided. 6 June 2007.
1(33)	Vol 3, B.5.2, analytical methods (residue) for food/feed of plant origin,	NL: An acceptable method for monitoring of residues of cyflufenamid in food/feed of plant origin is required, validated	RMS: See point 1 (32) above. The RMS concludes that the ILV is acceptable and a further method is not required.	Open point: The high RSD values for the residues in food method should be discussed in a

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)
	pg 37	according to SANCO/825/00. The submitted method displays unacceptable results (ILV).	Addressed.	meeting of experts and in general the level of validation in accordance with SANCO/825/00 should be considered. The applicant has stated that a justification will be provided. 6 June 2007.
1(34)	Vol 3, B.5.3.3, residues in air, pg 38	NL: Where does this long term AOEL come from? Under operator exposure in the LOEP only short term AOELs are mentioned and these are lower than the mentioned 0.03 mg/m^3.	RMS: This is an error. The value for the long term systemic AOEL of 0.01 mg/kg bw/day as given in Section B.6.10.3 (b) should have been used in this calculation. The correct concentration, C, is 3 µg/m^3. The LOQ of 1 µg/m^3 is still acceptable with respect to this revised concentration. Addressed.	Addressed: Rapporteur to consider in a revised DAR or corrigendum.
1(35)	Vol 3, B.5, analytical methods, pg 35	NL: In general descriptions of the analytical methods are too slim. Some form of discussion of the methods should be included, especially for the residue analytical method for food/feed of plant origin.	RMS: The RMS considers that the level of detail provided is sufficient. All methods were acceptable. A discussion of the specific issue relating to ILV of the method for food/feed of plant origin is included in the evaluation/assessment section of the method, Section B.5.5. For all other methods, there were no issues which required further discussion. Addressed.	See comment 1(31)
1(36)	Vol 4, C.1.4.1, analytical methods for impurities, pg 9	NL: The method cannot be accepted with the proposed LOQ's, because they do not allow determination of impurities at significant levels (from 1g/kg (0.1%w/w)).	RMS: The LOQs for the impurities are taken as the lowest concentration for which recovery and precision data were generated. In this case, the recovery levels determined the LOQ as these were performed at a higher level (0.15	See open point in comment 1(5).

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)
			%w/w in the majority of cases, but for two impurities it was 0.20 %w/w). Precision was determined at levels <0.1%w/w in all cases. The notified claimed that the recovery was performed at 50-140% of the certified limit for each impurity however the limits specified in the DAR are not consistent with this. Only two impurities were found above 0.1%w/w in the batch analysis. The specified limits for these impurities are adequately supported by the available data. For the other impurities, the RMS considers that the available data are sufficient to support the findings of the batch analysis – that these impurities are present at <0.1 %w/w. this consideration is based on the acceptable precision data at <0.1%w/w and the acceptable recovery data at three levels. These impurities are not included in the specification and therefore methods for their enforcement/monitoring are not required. Addressed	
1(37)	Further comment to Vol. 3, B.5.3.2 Residues in water Received during the written procedure	DE: The proposed enforcement method for drinking water is not valid for confirmation of positive findings. The use of m/z 188, 294 and 321 was validated for concentrations 100 times higher than 0,1 µg/l only. For filling this data gap notifier shall provide the study of Brewin, S. A. " NF-149 and Metabolites: Development and validation of methodology for the	The RMS agrees that the confirmation method was validated quantitatively at 100 times greater than the LOQ of the enforcement method, but considers that the requirements of the confirmatory method as defined in SANCO/3030/99 i.e. to demonstrate specificity, have been met and no further data are required. Addressed.	Open point: It should be discussed by a meeting of experts if the validation data for the confirmatory drinking water method is acceptable.

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)
		determination of residues in soils from three sites in Southern France, Northern France and Germany, and for the determination of residues in soil and water from a site in the UK", Report No. NOD 137/002147, Report No. RD-II02006.	The study of Brewin, S.A., 2000, NOD 137/002147, report no.RD-II2006 was submitted in the original dossier to support pre-registration studies, not as an enforcement method. The method determines residues of cyflufenamid and metabolites in leachate water by LC-MS at levels down to 0.05 µg/l.	

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(1)	NOT	Quality control data on technical cyflufenamid produced on an industrial scale manufacturing plant has been provided to RMS (UK PSD) on 6 June 2007. This data, together with analysis of 5 representative batches of such material, support a minimum purity of 980 g/kg of the active substance in the industrial scale technical product.	Noted info added to reporting table
1(5)	NOT	A study is being conducted to identify the LOQs in the method of analysis of the impurities in the technical active substance. The report is expected to be available end September 2007 and will be provided to the RMS.	Noted. But data for LOQ is not a requirement. The reporting table does not request further data.
1(32)	NOT	Communication between the primary laboratory and that chosen for the ILV is acceptable according to SANCO/825/00 rev.7, 17/03/2004. Justification for this has been provided to RMS on 6 June 2007.	Noted info added to reporting table
1(33)	NOT	The RSD values for the determined residues in food are within the limits specified in the EU guidance document (SANCO/825/00 rev.7, 17/03/2004). The justification for this has been provided to RMS (UK PSD) on 6 June 2007.	Noted info added to reporting table

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(36)	NOT	A study is being conducted to identify the LOQs in the method of analysis of the impurities in the technical active substance. The report is expected to be available end September 2007 and will be provided to the RMS.	Noted. But data for LOQ is not a requirement. The reporting table does not request further data.

2. Mammalian toxicology

Acute toxicity (B.6.2)				
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)
2(1)	Vol. 3, P70, B.6.2.5: Skin irritancy	NOT: In Vol. 3, page 70, B.6.2.5, liquid' in the second column (Dose & Nature) should be replaced with 'moistened solid'. Cyflufenamid is a solid and was moistened with distilled water for administration.	RMS: Agreed. Should state "0.5 g (moistened with distilled water)". Addressed.	Addressed RMS to consider in a revised DAR or corrigendum
2(2)	Vol. 3, P72, B.6.2.8: Summary of acute toxicity, irritancy and sensitisation	NOT: In Vol. 3, page 72, B.6.2.8, Table B.6.14 (line 6: skin irritation), the comment in Column 4 should be non irritant since no evidence of irritancy was found in the study (see B.6.2.5 on page 70).	RMS: Agreed. Should state "Not irritant". Addressed.	Addressed RMS to consider in a revised DAR or corrigendum

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 3, B.6.3.3 Oral short term studies in dogs, pg 88	EFSA: the higher sensitivity for "sex organs" effects in dogs is explained by the RMS as due to the increased clearance of hormones through induction of liver enzymes. The induction of liver enzymes was studied in rats and mice that, however, do not show such relevant effects on uterus, cervix, ovaries, epididymes and prostate. Further	RMS: The reference to increased sex hormone clearance is presented only as a possibility, and it is indicated in the DAR that this may be only part of the explanation for these findings (retarded growth/maturity also being possible explanations). It is not essential to clarify the mechanism and clear NOAELs for these findings are identified. Further discussion will not affect the risk assessment.	Addressed

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)
		discussion is needed on the subject.	Addressed.	
2(4)	Vol 3, B.6.3.3 Oral short term studies in dogs – Dog oral 12 month study, pg 88	EFSA: some of the "sex organ effects" in the 90 day study in dog are not found at comparable doses in the 12 month study in the same species.	RMS: See response to point 2(3). The lack of consistency in these findings further supports the proposal that further discussion of these findings will not affect the risk assessment. Addressed.	Addressed
2(5)	Vol. 1, list of end points	NL: RMS uses the NOAEL for brain vacuolisation in the 90 d dog study for setting the AOEL. This end point should, therefore, be included as a critical effect in short term studies in the list of end points.	RMS: Agreed. The list of endpoints have been amended. Addressed.	Addressed
2(6)	Vol. 3, P76, B.6.3.1 Oral studies in rats	NOT: In Vol. 3, page 76, B.6.3.1, it is stated in Liver (line 3) that 'Necropsy revealed a prominent hepatic lobular pattern of fat deposition (5/10 males…'. This should be amended to '**Necropsy revealed a prominent hepatic lobular pattern (5/10 males…) characterised microscopically as fat deposition**'. This is because histopathology is required to identify fat deposition.	RMS: Agree. The deposition of fat was confirmed by Oil Red O staining and microscopic examination. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum

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(7)	Vol. 3, P76, B.6.3.1 Oral studies in rats	NOT: In Vol. 3, page 76, B.6.3.1, it is stated that the testis was a target organ in the 28-day study. However, this was not identified as a target organ in the study report (RD-II01090). Only 1/5 males in each of the control and highest dose level (10800 ppm) exhibited degeneration of the tubular germinal epithelium (slight/moderate). Therefore the testis was not a target organ for toxicity in this rat 4-week dietary study.	RMS: Agree – there are no notable testes findings in the 4 week rat study. The only findings in the 4 week rat study relating to the male reproductive organs were in the prostate and seminal vesicles. Addressed.	Addressed
2(8)	Vol. 3, P79-80, B.6.3.1 Oral studies in rats	NOT: In Vol. 3, the last paragraph on page 79 which extends to page 80 should be transferred to page 136, B.6.5.3 Summary of chronic toxicity and carcinogenicity studies because it principally relates to setting the ADI.	RMS: Agree. This is a typographical error. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum
2(9)	Vol. 3, P81, B.6.3.1 Oral studies in rats	NOT: In Vol. 3, page 81, Table B.6.15 (last line), 'Liver: Lobular pattern of fat deposition' should be amended to '**Liver: prominent lobular pattern**' as this entry relates to macroscopic pathology. Fat deposition requires microscopy (histopathology) to be identified.	RMS: Agree. The description of this macroscopic finding should not refer to fat. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum

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(10)	Vol. 3, P81, B.6.3.1, Table B.6.15	NOT: The following are typographical errors in Table B.6.15: Blood urea nitrogen: insert units of measurement **(mg/dl)** Total bilirubin: amend units to **(mg/dl)** from (µg/dl) Calcium: amend units to **(mg/dl)** from (m/dl) Females terminal body weight at 300 ppm: amend to **294** from 299 Testis weight at 300 ppm: Delete ±	RMS: Agree for BUN (units missing). Total bilirubin values in Table B.6.15 have been converted from mg/dl in the study report into µg/dl in the DAR so the units are correct. Agree for calcium (typographical error). Agree for female bodyweight (this error originates in the Notifier's Tier II Summary document). Agree for testes weight (typographical error). Addressed.	Addressed RMS to consider in a revised DAR or corrigendum
2(11)	Vol. 3, P82, B.6.3.1, Table B.6.15	NOT: The following are typographical errors in Table B.6.15: Male myocardial vacuolation (total): insert **0** in 0 ppm column, "-" in 50 and 300 ppm columns, **0** in 1800 ppm column and **2** in 10800 ppm column Female myocardial vacuolation (slight): insert **0** in 0 ppm column and "-" in 50 and 300 ppm columns Female myocardial vacuolation (moderate): insert **0** in 0 ppm column and"-" in 50 and 300 ppm columns	RMS: Agree. To match the format of the remainder of the table. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum
2(12)	Vol. 3, P85, B.6.3.2 Oral short term studies in mice	NOT: In Vol. 3, page 85, B.6.3.2, replace 'rats' in line 1 of liver with '**mice**' since this section does not refer to rats.	RMS: Agree. Typographical error. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum

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(13)	Vol. 3, P88, B.6.3.2 Oral short term studies in mice, Table B.6.16	NOT: The following are typographical errors in Table B.6.16: Terminal body weight of males at 7000 ppm: amend to **36**±2 from 37±2 **Terminal body weight of females at 1600 ppm: amend to** 26±**2 from 27±2**	RMS: Agree. Typographical errors. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum
2(14)	Vol. 3, P89, B.6.3.2 Oral short term studies in mice [RMS comment: Please note the above comment refers to p89, B6.3.3 oral short term studies in dogs and not B.6.3.2]	NOT: Vol. 3, page 89, B.6.3.2, in Liver (paragraph 2, line 11), there are 2 typographical errors in the sentence 'Higher values were also recorded in females at 1000 and 4000 ppm (17-38%)…': i) replace 1000 with **2000** [ppm] and **ii) replace 17-38% with** 37-**38% .**	RMS: Agree – the current presentation is unclear. Cholesterol values in females in Week 4 were 138, 162 (+17%), 191 (+38%) and 188 (+36%) mg/dl at 0, 1000, 2000 and 4000 ppm respectively. There is an increase in each treated group, but the increases are greater at 2000 and 4000 ppm. None of the increases achieve statistical significance (though there are only 3 animals per sex per group) but more importantly there is no dose-response relationship. These results are not biologically significant compared to the results in males. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum
2(15)	Vol. 3, P92, B.6.3.3 Oral short term studies in dogs	NOT: In Vol. 3, page 92, paragraph 3, line 3, amend 'in males given 500 ppm 30%) to 'in males given 500 ppm **(**30%)'	RMS: Agree - typographical error. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum
2(16)	Vol. 3, P107, B.6.3.6 Summary of short term toxicity studies, Table B.6.20	NOT: In Vol. 3, page 107, Table 6.20, in row 10 (1-year dog dietary), column 1, amend highest dose level from 490 ppm to 480 ppm	RMS: Agree - typographical error. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum

Genotoxicity (B.6.4)				
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(17)	Vol. 3, P108, B.6.4.1 *In vitro* assays	NOT: In Vol. 3, page 108, B.6.4.1, paragraph 1, line 1 of a) Bacterial mutation assay, amend 'In a study (2001), ' to 'In a study (**2000**)…'.	RMS: Agree. The Notifier cover sheet for the Ames test is dated 2001, but the study itself was completed in 2000. All references to 'Kitching, 2001' should read 'Kitching, 2000'. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum
2(18)	Vol. 3, P109, B.6.4.1 *In vitro* assays	NOT: In Vol. 3, page 109, B.6.4.1, paragraph 1 line 1 of b) Chromosomal aberration assay, amend 'In a study (2001),… ' to 'In a study (**2000**)…'.	RMS: Agree. The Notifier cover sheet for this assay is dated 2001, but the study itself was completed in 2000 (and the author is mis-spelled). All references to 'Arkhurst, 2001' should read 'Akhurst, 2000'. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum
2(19)	Vol. 3, P111, B.6.4.2 *In vivo* studies	NOT: In Vol. 3, page 111, B.6.4.2, paragraph 1, line 1 of a) Micronucleus study in the mouse, amend 'In a study (2001,…. ' to 'In a study (**2000**,….'.	RMS: Agree. The Notifier cover sheet for this assay is dated 2001, but the study itself was completed in 2000. All references to 'Mason, 2001' should read 'Mason, 2000'. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum
2(20)	Vol. 3, P113, B.6.4.3 Summary of genotoxicity studies, Table B.6.21	NOT: In Vol. 3, page 113, B.6.4.3, Table B.6.21, in the Reference column of 'Reverse mutation test for bacteria', amend 2001 to **2000**	RMS: See points 2(17) and 2(18) for corrections to references in this table. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum
2(21)	Vol. 3, P113, B.6.4.3 Summary of genotoxicity studies, Table B.6.21	NOT: In Vol. 3, page 113, B.6.4.3, Table B.6.21, in the Reference column of 'Mammalian cytogenetic test', amend 2001 to 2000.	RMS: See points 2(17) and 2(18) for corrections to references in this table. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum

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(22)	Vol. 3, P115, B.6.5.1 Oral study in rats (Long-term toxicity and carcinogenicity)	NOT: In Vol. 3, page 115, B.6.5.1, Liver, second paragraph, line 4 amend 'Week 13 (21% depression)' to 'Week 13 (**11**% depression)'	RMS: Agree – typographical error. This error does not affect the NOAEL for the study. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum
2(23)	Vol. 3, P125, B.6.5.2 Mouse (carcinogenicity study)	NOT**:** In Vol. 3, page 125, B.6.5.2, line 3 of Animals killed or dying – week 20 to termination, amend 'A lower incidence of pale skin…' to 'A lower incidence of **skin masses**…'.	RMS: Disagree – the statement is correct. Incidences of pale skin were decreased in these animals (compared to females killed or dying during weeks 1 to 19 which often showed this finding). The same statement is made in the study summary. Addressed.	Addressed
2(24)	Vol. 3, P127, B.6.5.2 Mouse (carcinogenicity study), Table B.6.24	NO**T:** In Vol. 3, page 127, B.6.5.2, Table B.6.24, for <u>males fed 0 ppm</u>: Terminal body weight, amend 57.7 to **57.4** Periportal/centrolobular fat deposition, amend 4 to **11**	RMS: Agree – typographical error. This error does not affect the interpretation of the study. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum
2(25)	Vol. 3, P127, B.6.5.2 Mouse (carcinogenicity study), Table B.6.24	NOT**:** In Vol. 3, page 127, Table B.6.24, for <u>females fed 4000/2000 ppm</u>: Fat deposition in cortical tubular epithelium, amend 10 to **10*** Bronchiolar-alveolar carcinoma, amend 3* to **3**	RMS: Agree – typographical errors. These errors do not affect the interpretation of the study. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum
2(26)	Vol. 3, P132, B.6.5.2 b) Supplementary oral carcinogenicity study, Table B.6.26	NOT**:** In Vol. 3, page 132, B.6.5.2, Table B.6.26, Liver – marked enlargement, amend values from 7, 15, 5, 2 to **0, 4, 4, 7**	RMS: Agree – typographical errors. These errors do not affect the interpretation of the study. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum

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(27)	Vol. 3, P135, B.6.5.3 Summary of chronic toxicity and carcinogenicity studies	NOT: In Vol. 3, page 135, B.6.5.3, Thyroid tumours (rats), line 6, delete 'disturbance of the'. The change in thyroid activity was the consequence of the normal negative feedback mechanism.	RMS: Agree – prolonged increased TSH release by the pituitary as a result of reduced plasma thyroid hormone levels does not involve disruption of the feedback mechanism. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum

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(28)	Vol. 3, P137, B.6.6.1 Multigeneration study in rats	NOT: In Vol. 3, page 137, B.6.6.1, in paragraph 3, delete '0' at the start of line 2 and amend font size of paragraph 2 of F0 generation findings.	RMS: Agree – typographical errors. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum
2(29)	Vol. 3, P138, B.6.6.1 Multigeneration study in rats	NOT: In Vol. 3, page 138, B.6.6.1, in Conclusions, amend font size of 'in' in line 2. Also, delete '/or' in this line.	RMS: Agree – typographical error. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum
2(30)	Vol. 3, P138, B.6.6.1 Multigeneration study in rats, Table B.6.28	NOT: In Vol. 3, page 139, B.6.6.1, Table B.6.28, in Achieved test material intake during lactation (females) at 800 ppm, amend 12 to **125**	RMS: Agree – typographical error. This error does not affect the interpretation of the study. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum
2(31)	Vol. 3, P140, B.6.6.1 Multigeneration study in rats, Table 6.28	NOT: In Vol. 3, page 140, B.6.6.1, Table B.6.28, delete the last 5 rows as they are duplicated items.	RMS: Agree – typographical error. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum

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(32)	Vol. 3, P147, B.6.6.4 Summary of reproductive toxicity studies, Table 6.31	NOT: In Vol. 3, page 147, B.6.6.4, Table B.6.31, in Rabbit developmental toxicity, amend ' batch T3G-1020; 95.2%' to 'batch T3G-1020; 95.4%'	RMS: Agree. It should be made clear that batch T3G-1020 used in the reproductive studies was re-analysed in November 1999 before the later rabbit study was performed – the value of 95.4% was obtained at that analysis which is why a different purity value is quoted for this batch in the later study. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum

Other toxicological studies & Medical data (B.6.8-B.6.9)				
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)
2(33)	Vol. 3, B.6.8.2.3 (p 182), Summary of the toxicity studies conducted with the metabolites	EFSA: The arguments provided to demonstrate the non toxicological relevance of metabolites 149-F1 and 149-F6 need to be further considered based on the results of the acute toxicity testing (higher toxicity than cyflufenamid) and the lack of information on the long term toxicity. This is supported by the findings in the residue section (they are major metabolites in food of animal origin).	RMS: Evaluation of the relative toxicity of these two metabolites appears in Section B.6.8.2.3 (page 182). It is suggested that the increased acute toxicity will only be relevant to high dose levels (evidence being the nervous system effects seen at high dose levels only). 149-F1 and 149-F6 are both rat metabolites, and 149-F1 in particular is excreted in significant amounts (14% in urine), with 149-F6 up to 3% in urine. The significant in situ generation of 149-F1 is important since this is the predominant part of the residue in most animal product matrices (though all residues are expected to be low for the supported use). The long term toxicity of these metabolites	Open point MSs to discuss the relevance of metabolites 149-F1 and 149-F6

Other toxicological studies & Medical data (B.6.8-B.6.9)				
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)
			(particularly 149-F1) should have been taken into account in the long term studies with cyflufenamid due to this significant in situ generation. If it is necessary to include these metabolites in the residue definition for animal products (due to significant residues being expected for a particular use), then it would be appropriate to perform the risk assessment against the ADI and ARfD for cyflufenamid since the toxicity of these metabolites should have contributed to the NOAELs used to derive these values (due to the in situ generation described above). Since the toxicity of these metabolites has been tested within the cyflufenamid studies, and since the NOAELs in cyflufenamid studies are not especially low compared to the NOAELs of other pesticides, there is no reason to apply lower than default thresholds of concern for residues of these metabolites (i.e. the normal 0.01 mg/kg threshold for residues of these metabolites should be applied). This could be discussed at a Toxicology Expert Meeting if considered necessary by the Residues Expert Meeting. Open point	

Other toxicological studies & Medical data (B.6.8-B.6.9)				
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)
2(34)	Vol. 3, P154, B.6.8.1.2 Enzyme studies, Table B.6.34	NOT**:** In Vol. 3, page 154, B.6.8.1.2, Table B.6.34, in 'Difference Day 0-14' for 0 ppm: Total BALP3 amend from 3.1± 1.8 to **-3.1± 1.8** LALP amend from 62.2± 15.9 to **-62.2± 15.9**	RMS: Agree – typographical errors. These errors in the table do not affect the interpretation of the study (the findings are correctly described in the text). Addressed.	Addressed RMS to consider in a revised DAR or corrigendum
2(35)	Vol. 3, P160, B.6.8.1.3 Hormonal studies	NOT: In Vol. 3, page 160, B.6.8.1.3, delete the last sentence since the fluctuations in testosterone level in all treated groups were within the variable ranges for the controls at each sampling time. The rationale for the Leydig cell hypertrophy seen at the highest dose level, 108000 ppm, is unclear.	RMS: It is acknowledged that testosterone levels are very variable in control and treated groups. Examination of the individual animal data shows that the values in the 100 ppm group are mostly within the range of the control values, and often the mean values for a group are markedly influenced by a single very high or very low outlying value. Clear conclusions about possible testes effects at 100 ppm cannot be drawn from the testosterone data alone, and no attempt is made to draw such conclusions in the Summary of Supplementary Studies at Section B.6..8.1.5. Histopathological findings in the testes were restricted to very high dose levels and further discussion of these high dose effects will not affect the risk assessment. Addressed.	Addressed
2(36)	Vol. 3, P175, B.6.8.1.5 Supplementary studies with the active substance, Table B.6.41	NOT: In Vol. 3, page 175, B.6.8.1.5, Table 6.41, in first column of row 1, amend 'Rat medium-term rat carcinogenesis bioassay' to 'Rat medium-term carcinogenesis bioassay'	RMS: Agree – typographical error. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum

Other toxicological studies & Medical data (B.6.8-B.6.9)				
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)
2(37)	Vol. 3, P175, B.6.8.1.5 Supplementary studies with the active substance	NOT: In Vol. 3, page 175, B.6.8.1.5, paragraph 1, line 7, delete 'of disturbance'. Negative feedback is a normal mechanism. In line 9, amend 'Thus the thyroid follicular cells seen in…' to 'Thus the thyroid follicular cel**l adenomas** seen in…'.	RMS: See point 2(27). Agree with "thyroid follicular cell adenomas" (typographical error). Addressed.	Addressed RMS to consider in a revised DAR or corrigendum
2(38)	Vol. 3, P178, B.6.8.2.1 Acute oral toxicity of the metabolites	NOT: In Vol. 3, page 178, B.6.8.2.1, in Mortality (per dose respectively) for 149-F11, amend line 2 from '2/5 then 4/5 (females)' to '2/5 then **0** (females)**'**.	RMS: Agree – typographical error. This error in the table does not affect the interpretation of the study (the findings and LD_{50} values are correctly described in the text and the summaries). Addressed.	Addressed RMS to consider in a revised DAR or corrigendum
2(39)	Vol. 3, P179, B.6.8.2.1 Acute oral toxicity of the metabolites	NOT**:** In Vol. 3, page 179, B.6.8.2.1, Mortality (per dose respectively) for line 3 amend 'Deaths occurred within 1 day of dosing' to 'Deaths occurred 1-5 days after dosing'.	RMS: Agree – typographical error. This error in the table does not affect the interpretation of the study. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum

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(40)	Vol 3, B.6.10. 1/2/3 ADI, AOEL, ARfD (pg187)	EFSA: the relevant NOAELs to set reference values and the uncertainty factor applied need to be further discussed, due to the specificity of some of the end points	RMS: See points 2(41), 2(42) and 2(43). Open Point.	Open point Reference values to be discussed in an experts' meeting, taking into account relevant effects (in particular the

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)
		considered (e.g. brain vacuolation) and to the different sensitivity of the species investigated.		occurrence of brain vacuolation)
2(41)	Vol 3, B6.10.1 and Vol. 1, 2.3.2 (pg 15) and list of endpoints, ADI	DE: Proposal: We propose to derive the ADI based on the NOAELs (both ca. 4 mg/kg bw/d) in the chronic toxicity / carcinogenicity study with rats and the 1-yr dietary study with dogs. The usual safety factor of 100 should be applied. This ADI (0.04 mg/kg bw) would be 575-fold lower than the NOAEL for brain vacuolisation seen in the 13-wk study with dogs.	RMS: The rationale for selecting the NOAEL for brain vacuolation and the higher safety factor for the ADI are presented in Section B.6.10.1. The main concerns are the potentially severe nature of this finding (if it is relevant for humans), and the fact that there is uncertainty over whether it is reversible. The reversibility of brain vacuolation was only demonstrated in animals maintained for a 26 week recovery period (not 13 weeks recovery), and the group size was small (3 females only). It is felt necessary to ensure at least a 1000-fold margin over the NOAEL for this effect. The size of the safety margin and the choice of NOAEL for the ADI should be confirmed at an Expert Meeting. Open Point.	See 2(40)
2(42)	Vol 3, B6.10.3 and Vol. 1, 2.3.4 (pg 16) and list of endpoints, AOEL	DE: Proposal: (A) Only one AOEL should be derived. (B) We propose to derive the AOEL based on the NOAEL (6.5 mg/kg bw/d, 150 ppm) in the 13-wk dietary study with dogs. The next higher dose level led to reduced body weight gain and liver toxicity. The usual safety factor of 100 and correction for oral absorption (70%) should be applied.	RMS: The rationale for selecting the NOAEL for brain vacuolation and the higher safety factor for the AOEL are presented in Section B.6.10.3. The concerns relating to the brain vacuolation effect in dogs are the same as presented in the response to point 2(41) for the ADI. If it was chosen not to apply a larger safety margin to the brain vacuolation effects,	See 2(40)

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)
		This AOEL-S (0.05 mg/kg bw/d) would be 460-fold lower than the NOAEL for brain vacuolisation seen in this study.	then the AOEL proposed by Germany would be appropriate. This should be discussed at an Expert Meeting. Open Point. If the NOAEL of 6.5 mg/kg bw/day based on liver toxicity is used then the 70% correction for oral absorption is appropriate. See point 2(44) for discussion of oral absorption when the brain vacuolation NOAEL is used.	
2(43)	Vol 3, B6.10.3, pg 193 and Vol. 1, 2.3.3 (pg 16) and list of endpoints, ARfD	DE: Proposal: Maternally toxic effects seen at 10 mg/kg bw/d (lower body weight gain and reduced feed intake) in one rabbit developmental study were not confirmed by the other rabbit developmental study. Therefore we propose to use a NOAEL of 10 mg/kg bw/d to derive the ARfD. The usual safety factor of 100 should be applied, leading to an ARfD of 0.1 mg/kg bw/d.	RMS: Disagree. It is unclear why different effects on food consumption were seen at 10 mg/kg bw/day in the two rabbit studies (same methods, same batch of test material – similar purity on re-analysis – 95.2 to 95.4%). As a conservative approach the DAR proposed 5 mg/kg bw/day as the clear NOAEL for maternal toxicity in these rabbit studies. The appropriate NOAEL could be discussed at an Expert Meeting. Open Point.	See 2(40)
2(44)	Vol. 3, B.6.10.3, AOEL, pg 192	NL: The proposed AOEL is based on the NOAEL for brain vacuolisation in a 90 day oral study with the dog (23 mg/kg bw/day). A correction for oral absorption of 70% is applied. However, excretion in bile was 61-77%. Enterohapic cycling occurs, but urinary excretion in non cannulated rats was 31%(males) 18% (females). Therefore, the target organ (brain) will not have seen a large part of	RMS: It is agreed that the correction for oral absorption (when the NOAEL for brain vacuolation is used) should be considered further. The draft Guidance Document on Setting AOELs (rev.10, 7 July 2006) states that where the critical target organ is not the liver (or the GI tract) and the biliary component is unlikely to have reached the target organ due to rapid excretion, then exclusion of the biliary component should be considered. However, in	See 2(40)

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 biliary component and a greater reduction factor should be applied for calculating the AOEL based on brain vacuolisation. 18% systemic availability is proposed, based on urinary excretion, cage wash and carcas in females of the SOLD group.	this case there is evidence that at least some of the biliary component would have been systemically available to reach the brain and it is not considered appropriate to exclude the entire biliary component for the following reasons. The following assumes that ADME in rats is comparable to dogs (and humans) – without ADME data from dogs no other assumption is possible. The low dose ADME data for bile duct cannulated rats does not indicate "rapid excretion" via bile as referred to in the draft AOEL Guidance Document. Table B.6.2 in the DAR indicates ≈20-30% excretion via bile up to 6 hours, which could be described as reasonably rapidly excreted and could be excluded as suggested by the Guidance Document. However, excretion via bile continues in significant amounts such that ≈40-45% of the dose is excreted in the period 6-48 hours after dosing. The question arises where is this 40-45% of the dose located over the first 6 hours after dosing and beyond until it is eventually excreted over 24 to 48 hours? The plasma concentration curves (Figure B.6.2) suggest rapid absorption of a low dose from the stomach/GI tract (an early peak of absorption with T_{max} 1-4 hours) so this 40-45% does not appear to be lying	

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)
			unabsorbed in the stomach/GI tract for the first few hours. The tissue distribution data indicates a substantial amount of material in the liver after 4 hours (reflecting the ≈20-30% excreted via bile in the first few hours?). It is not known what proportion of the 40-45% is retained in the liver and never reaches the systemic circulation. The fact that <0.5% of the dose remains in the liver of cannulated rats after 48 hours (equivalent to the amount in the GI tract and less than the amount in the remaining carcass) argues against highly effective retention/accumulation of material in the liver and in favour of dose "passing through" the liver via bile. It is therefore possible that some proportion of the 40-45% of dose not rapidly excreted via bile (possibly all of it) will have been systemically available to a significant extent. Taking all bile excreted from 6 hours onwards plus urine from cannulated rats as representing systemically available material would give an oral absorption value of ≈50% for both sexes. Using the NOAEL of 23 mg/kg bw/day for brain vacuolation and the 1000-fold safety margin as proposed in Section B.10.3, then applying a revised oral absorption correction of 50% would give a revised short term AOEL of 0.012 mg/kg bw/day. If the proposal of the Netherlands to use 18% oral absorption was accepted, the AOEL would	

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)
			be 0.004 mg/kg bw/day. If the proposal to base the AOEL on the NOAEL for liver effects (point 2(42)) was accepted, then a 70% oral absorption correction (based on all material excreted in bile) would be appropriate (which would give 0.05 mg/kg bw/day). The appropriate value to use for oral absorption (and the NOAEL) should be discussed in an Expert Meeting. Open Point.	
2(45)	Vol. 1, P15, 2.3.2: Proposal for acceptable daily intake (ADI) Vol. 1, P75, 3.1 Background to proposed decision Vol. 3, P79, B.6.3.1: Conclusions Vol. 3, P192, B.6.10.1: Acceptable daily intake	NOT: In Vol. 1, page 15, line 5 of 2.3.2 (line 5), on page page 75, 3.1 (paragraph 8, line 5), and in Vol.3, page 79, B.6.3.1 (line 6 of the last paragraph) and page 192, B.6.10.1 (line 5), it states that 'However, potentially severe and irreversible effect, brain vacuolation, was seen in the dog 90 day study (23 mg/kg bw/day)'. But reversibility was demonstrated in the dog 90 day study with 26 week recovery period (study report RD-II01115); see item 2 below. Therefore 'irreversible' should be replaced with '**reversible**'.	RMS: There is considered to be uncertainty over the reversibility of the brain vacuolation findings. Reversibility was only demonstrated in a study with a small number of animals (3). See response to point 2(41). The significance of the brain vacuolation findings should be discussed in an Expert Meeting. Open Point.	Open point The relevance of brain vacuolation to be discussed in a meeting of experts. See also 2(40)

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(46)	Vol. 1, P15, 2.3.2: Proposal for acceptable daily intake (ADI) Vol. 1, P75, 3.1: Background to the proposed decision Vol. 3, P192, B.6.10.1: Acceptable daily intake Vol. 3, P 99, B.6.3.3: 90-day dog with 26 week recovery period, Microscopic pathology Vol. 3, P107, Table B.6.20: Summary of short term toxicity studies with cyflufenamid	NOT: In Vol. 1, page 15, 2.3.2 (line 8), on page 75, 3.1 (paragraph 8, line 8) and in Vol.3, page 192, B.6.10.1 (paragraph 1, line 8), add '**evidence of reversibility was seen 26 weeks after cessation of dosing**' at the end of the phrase 'not drive the NOAELs in the 90 day and 1 year dog studies'. Reversibility was demonstrated in the dog 90-day study with 26 week recovery period (study report RD-II01115) and is stated in Vol. 3, page 99, B.6.3.3 in Microscopic pathology (last line) and on page 107, Column 3, Table B.6.20 (90-day dog dietary with 26 week recovery period).	RMS: See point 2(45).	See 2(40)
2(47)	Vol. 1, P15, 2.3.2 and P76, 3.1: Proposal for acceptable daily intake (ADI) Vol. 3, P 192, B.6.10.1: Acceptable daily intake Vol. 3, P 99, B.6.3.3: 90-day dog with 26 week recovery period	NOT: In Vol. 1, page 15, 2.3.2 (line 12) and on page 76, 3.1 (line 3) and in Vol. 3, B.6.10.1 (line 12), it is stated that the 'reversibility of the brain lesion seen in dogs has not been elucidated'. But, on the last line of page 99 of Vol. 3, B.6.3.3, it is stated that 'No brain lesions were seen in any animal killed after the 26-week recovery period [following a 90-day treatment period]'. See also the dog 90-day study with 26 week recovery period	RMS: See point 2(45).	See 2(40)

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)
	Vol. 3, P107, Table B.6.20: Summary of short term toxicity studies with cyflufenamid	on Table B.6.20 on page 107 and Notifier's report of this study (no. RD-II01115. Therefore reversibility of these lesions was demonstrated.		
2(48)	Vol. 3, P190, B.6.10 Summary of mammalian toxicology and proposed ADI, AOEL, ARfD and MAC, Table B.6.43	NOT: In Vol. 3, page 190, B.6.10, Table 6.43, line 2 of last row (1-year dog dietary), amend 0, 30, 120, 490 ppm to 0, 30, 120, **480 ppm**.	RMS: Agree - typographical error. Addressed.	Addressed RMS to consider in a revised DAR or corrigendum

Toxicity of the product(s) (B.6.11)				
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(49)	Vol. 3, B.6.11.d) pg 196, Skin irritancy and Vol. 1, 2.1.4.2 (pg 12)	DE: In view of slight erythema being still present in two animals at study termination on day 14, the preparation should be labelled with R38 (irritating to skin) and because of the content of solvent (Solvesso 200 ND) in the preparation, for the classification and labelling R65 should be considered additionally.	RMS: Classification with R38 (Irritating to skin) is required. The calculation of erythema scores presented in the DAR is incorrect. The correct value is 2.06 which exceeds the threshold for classification regardless of the effects which persist to termination. The Endpoints have been revised. Classification with R65 is justified due to the amount of aromatic hydrocarbon solvent present in the preparation. The physical-chemical properties data available (viscosity and surface tension) do not allow this classification to be excluded because the tests have not been performed at the correct	Addressed Classification and labelling of preparations to be dealt with at MS level

Toxicity of the product(s) (B.6.11)				
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)
			temperature. Addressed.	

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(50)	Vol 3, B.6.12 and Vol. 1 (pg 70), list of endpoints, Dermal absorption	DE: Proposal: Dermal absorption should be re-evaluated. We propose 1 or 8% dermal absorption for the concentrate or the dilution, respectively.	RMS: Agree. The amount remaining in the skin at the end of the *in vitro* study should be included as absorbed. In the absence of skin stripping of the outer layers of skin this may represent a slight overestimate but this will not be excessive since the material removed by swabbing again after 24 hours has been excluded as not absorbed. The proportions of dose absorbed for the spray dilution were therefore 45.32% (rat) and 29.52% (human), meaning rat skin was 1.54 times more permeable to diluted material. The proportions of dose absorbed for the undiluted material were 19.35% (rat) and 3.87% (human), meaning rat skin was 5 times more permeable to undiluted material. Applying correction factors of 1.54 and 5 to the results of the rat *in vivo* penetration study (12% for in-use dilution and 5% for undiluted formulation) gives the dermal penetration indicated by Germany – 8% for the dilution and 1% for the concentrate.	Addressed

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)
			This proposal is considered to be more robust and transparent than the proposals currently presented in the DAR, and is justified since material continues to be absorbed from the skin at a significant rate even after washing of the skin surface has taken place. These proposals are also in line with the SANCO Guidance Document. The List of Endpoints have been revised. These proposals could be discussed at an Expert Meeting. Open point Assuming the higher value of 8% for dermal absorption for the spray solution, the predicted exposures would be within the AOEL for operators not wearing PPE, bystanders and Re-entry workers. An addendum reflecting this higher dermal absorption value has been provided by the RMS. With regards to point 2(40) these predicted exposures may be compared against an alternative systemic AOEL to that used for the exposure assessments should one be agreed	

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(51)	Vol 3, B.6.14, Exposure data (pg 201)	DE: Comment: The German proposals for the AOEL and the dermal absorption differs from the RMS proposal (see above). Therefore, the risks for the operator, worker and bystander were reevaluated for both possibilities with German consumption data. On the basis of the proposed dermal absorption rates of 1 % and 8 % [see 2(50)] and a systemic AOEL of 0.05 mg/kg bw/d [see 2(43)], the operator, worker and bystander exposure would also be acceptable	RMS: AOEL and dermal absorption values to be discussed at an Expert Meeting. Revised risk assessments can be presented once values are agreed. The UK agrees with these conclusions (see 2(5)). Open Point.	See 2(40)
2(52)	Vol. 3, P201, B.6.14.1.1 Estimation of operator exposure	NOT: In Vol. 3, page 201, B.6.14.1.1, at the end of the second sentence in the paragraph 2, add '**of 0.7 and a 1000 fold safety factor**' since these values are relevant to this section on the estimation of operator exposure.	RMS. Agree. Addressed in Addendum. These values relating to the AOEL are to be discussed at an Expert Meeting – see point 2(44). Addressed.	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)
2(53)	General comment	EFSA: the composition of the two representative batches used in tox studies is reported in Vol. 4. The proposed technical specification shows small differences if compared to the batches analysed. RMS to confirm that the tox	RMS: The batch used in almost all the toxicology studies was T3G-1020, and information on the composition of this batch has been provided. The batch tested in the studies is less pure (95.5%) than the proposed technical specification (min.97.0%) which means the toxicology tests will generally represent the	Open point MSs to agree on the representativeness of batches used in tox studies to the proposed specification

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)
		package adequately "covers" the potential toxicity of the technical specification.	"worst-case" with respect to impurities. There is an impurity at 0.7% in the toxicology batch compared to 1.0% in the technical specification. This impurity is a stereoisomer of cyflufenamid and has been tested (see Section B.6.8.2) in an acute oral toxicity study (LD_{50} >5000 mg/kg bw) and an Ames test (negative result). The similar structure and the results of these two studies would be considered sufficient in themselves to justify an increase from 0.7% tested in toxicology studies to 1.0% in the technical specification. In this case there is also the added reassurance that this substance was also tentatively identified in the rat metabolism study (it may be in equilibrium with cyflufenamid, but with the equilibrium very strongly favouring cyflufenamid). There is also an impurity at 0.13% in the toxicology batch compared to 0.3% in the technical specification. This impurity is also a postulated metabolite in the rat following cyflufenamid treatment, and has been shown to be naturally occurring in rats and extensively studied in the scientific literature e.g. LD_{50} >2000 mg/kg bw (see Kawai, 2002a – summarised in Appendix 4A in the DAR). There are no concerns regarding this substance at 0.3% in the technical specification. 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)
2(54)	Vol. 3, Appendix 4, Mammalian toxicology references	NOT: In Vol. 3, page 443, Appendix 4, there is no summary of the independent report on the neurotoxicity of cyflufenamid prepared by an international panel of expert neurotoxicologists and neuropathologists. This is considered to be critical to the DAR and so needs to be included.	RMS: The "independent report" referred to was a panel of expert neuropathologists and neurotoxicologists which was convened by the Notifier to review the cyflufenamid data. The panel reviewed the toxicity and metabolism data, and also the histopathological slides and electron micrographs of the dog brains. The panel concluded that the dog brain lesions were unique in their experience, but there were clear NOELs in each study, no similar lesions in mice or rats and the panel considered that no further data were necessary. The experts for this panel were selected and paid by the Notifier. No new data or scientific arguments were introduced in this report. The report confirms the findings and NOAELs reported in the DAR for these lesions, but does not add anything further. Addressed.	Addressed

Comments received on reporting table, section Mammalian Toxicology (B.6)			
Reference to reporting table	MS / Notifier	Comment	EFSA response
		No comments received	

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 and Vol. 3, B.7.1.2 Wheat metabolism (A) and (B/C) (pg218)	EFSA: Please indicate the number of days between treatments and sampling/harvest and possibly the growth stage at harvest as this is considered useful information to compare the metabolism study with the actual GAP/ field trials.	RMS: In the DAR the times of treatment are stated in terms of growth stage. The times of treatment in the metabolism studies A and C (treatments made at GS 32 and 59) seem more applicable to the requested GAP than for study B (treatment made at GS 32 and 39). In all studies two treatments have been applied and this is in line with the requested GAP. Metabolism studies are usually regarded as semi-quantitative with precise GAPs not needing to be adhered to, and these studies, overall when considered together, are considered sufficiently representative of the requested GAPs. GAPs for cereals are commonly expressed in terms of GS rather than number of days especially when the time of treatment is at these earlier growth stages. With reference to study A, the growth stages at the various sampling intervals were not stated. The final harvest time was 'at maturity'. The 2nd application was 38 days after the 1st application. The final harvest was 53 days after the 2nd application and 91 days after the 1st application. With reference to study B, the growth stages at the various sampling intervals were not stated. The final harvest time was 'at maturity'. The	Addressed Information to be transferred into an addendum/ corrigendum as appropriate

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)
			2nd application was 33 days after the 1st application. The intermediate sampling for immature heads, straw and roots was 37 days after the 2nd application and 70 days after the 1st application. The final harvest was 77 days after the 2nd application and 110 days after the 1st application. With reference to study C, the growth stages at the various sampling intervals were not stated. The final harvest time was 'at maturity'. The 2nd application was 38 days after the 1st application. The intermediate sampling for immature heads, straw and roots was 29 days after the 2nd application and 67 days after the 1st application. The final harvest was 53 days after the 2nd application and 91 days after the 1st application. Addressed.	
3(2)	Vol. 3, B.7.1.1 Wheat metabolism (A), Table B.7.2 (pg218)	EFSA: The header of the table B.7.2 seems to be incomplete. Therefore the meaning of some of the presented figures remains unclear. Please clarify.	RMS: The table B.7.2 is confusing and incomplete due to the table header becoming mixed up in the final version of the DAR. The five numeric columns of the table should be headed (left to right): ERR aqueous methanol extraction %TRR; ERR aqueous methanol extraction mg/kg; RRR %TRR; RRR mg/kg; total mg/kg. Addressed	Addressed RMS to provide the corrected table in an addendum/ corrigendum as appropriate

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(3)	Vol. 3, B.7.1.1 Vol. 3, B.7.1.2 Wheat metabolism (A) and (B/C) and Vol.3, B.7.1.4 Summary/assessment (pg218)	EFSA: Even though reported as metabolite 149-(E)- FB it was not explicitly mentioned that this compound is the E-isomer of parent cyflufenamid (Z-isomer). Given the reported high purity (99% or greater) of the test material in the metabolism studies (provided the values refer also to the isomeric purity) the discovered 3-4% E-isomer in the analysed forage and straw samples should be explained. As 149-(E)- FB is called a metabolite, does this mean that isomerisation occurred due to metabolic activity in the plants?	RMS: The purity reported in the studies and DAR is for radiochemical purity (as measured by HPLC with radiodetection); and no breakdown is given in terms of composition of E versus Z isomer; the chromatogram however shows a single peak named 'NF-149'. Therefore, although not confirmed, it is possible that some isomerisation has taken place in the metabolism study. Addressed	Open point RMS to elaborate further on whether isomerisation into the Z-isomer has taken place and if so, to clarify the impact on the risk assessment in an addendum
3(4)	Vol. 3, B.7.1.2 Wheat metabolism (B/C) (pg222)	EFSA: Is there any idea of what the unknown grain residues (46% TRR) could be?	RMS: Table B.7.6 shows solvent extractabilities showing that the majority of residues were found either in the methanol or the aqueous fractions (rather than in hexane or ethyl acetate). The identity of the grain metabolites was not elucidated (parent was found) however the 46% (= 0.017 mg/kg) was reported in Table B.7.8 to be 6 unknowns, individually in the range of <0.0001-0.008 mg/kg. Addressed.	Addressed Information to be provided in an addendum/ corrigendum as appropriate
3(5)	Vol. 3, B.7.3 (pg 220) and Vol. 1, 2.4.1 (pg 17) and list of endpoints, Definition of the residue (animal matrices)	DE: Proposal: We propose to derive a residue definition for animal matrices from the goat metabolism study although no residues above 0.01 mg/kg will be expected as a result of submitted applications to cereals. Since the parent compound was the only relevant residue	RMS: The RMS proposal is that it acceptable to not set a residue definition for animal products at the current time (it is not considered that individual residues above 0.01 mg/kg would be expected as a result of the GAP use) and then set a residue definition for animal products for	Open point To be discussed in an experts' meeting whether a, and if so what, residue definition for risk assessment and monitoring for food of animal origin should be proposed

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)
		in the goat metabolism study we propose to appoint cyflufenamid as residue definition for animal matrices.	future extensions of uses if residues are expected to be found at higher levels in animal products. UK RMS toxicological advice is that the relative toxicity of metabolites and the toxicological profile of parent is such that residues of metabolites and parent individually up to 0.01 mg/kg would not be expected to be of concern (see section B.6.8.2.3). The RMS agrees that animal product residues are not expected as a result of the currently proposed use. [However it is considered that if a residue definition is considered necessary at the current time on the basis of the animal metabolism data then the residue definitions should be set for both monitoring purposes and for risk assessment as: cyflufenamid and metabolite 149-F1 (UK RMS toxicologist advice is that metabolite 149-F1 is of relevance toxicologically compared to parent, at least on an acute basis, and metabolite 149-F1 is of higher acute toxicity than metabolite 149-F6, and 149-F1 is the predominant metabolite in the animal metabolism)] Addressed	The meeting consider aspects such as fat solubility of parent compound, toxicological relevance of metabolites 149-F1, 149-F6 (higher acutely toxic) see also comments 3(6), 3(7), 3(8), 3(9), 3(10), 3(11)

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(6)	Vol.3, B.7.2.2 Goat	EFSA: The major metabolites and main	RMS: All individual residues are expected to be	Refer to open point in 3(5)

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)
	metabolism (pg238)	residues in food of animal origin, in particular milk, kidney, liver, muscle, are 149-F1 and 149-F6. (together up to 75% TRR) Given the higher acute toxicity when compared to parent and the fact that no chronic toxicity data for the two metabolites are available, the RMS' conclusion that they were of no toxicologically relevance and should not be included in the residue definition/ in the consumer risk assessment.	<0.01 mg/kg. Therefore at the current GAP rates, no residues are regarded as of toxicological concern (even taking account of the N expression proposed by EFSA in point 3 (7) below). - see above preference for the residue definition, if it is considered that one should be proposed at this time (the UK considers that this should not be necessary). Addressed.	
3(7)	Vol.3, B.7.2.2 Goat metabolism (pg238)	EFSA: When compared on a dry matter basis (intake beef cattle 0.366 mg/kg) the overdosing factor in the goat study is 3.3 N for the low dose and 36N for the high dose. Moreover, there is always some uncertainty in extrapolation from higher dose levels. Therefore, residues exceeding 0.01 mg/kg in food of animal origin (in particular liver) can not be generally excluded. Then, the toxicological relevance of 149-F1 and 149-F6 should be further elucidated.	RMS: the UK DAR has calculated N rates in relation to wet weight expression. However considering the most relevant low dose the N rates are still similarly exaggerated according to either expression (3.3N dry matter expression 3.8 N wet weight expression). At this lowest dose, the overall TRR in milk, fat, kidney, liver, and muscle was 0.004, 0.014, 0.015, 0.113, and 0.003 mg/kg. Given the breakdown of residues in the liver at this dose rate (149-F1 at 0.016 mg/kg and 149-F6 at 0.034 mg/kg) it is not considered that significant residues of these metabolites would be expected at normal dose rates that could arise from GAP use. Although the parent molecule has a relatively high log Pow value, the metabolism data shows that in practice that parent constituted <10% of the overall residue in milk; also total residues in fat and milk were very low.	Refer to open point in 3(5)

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)
			Although the metabolism study was dosed for five days, a plateau appeared to be reached in milk after two days. The evidence based on metabolism data is considered more relevant than the potential indication of log Pow. Also five days is considered a relevant dosing period for a metabolism study. In this case a longer term feeding study is not considered necessary. Addressed.	
3(8)	Vol. 1, Level 2, Appendix 3, List of End Points, Metabolism in livestock (pg 71)	NL: See also comment (1). Animal residue definition for monitoring: Not required. Animal residue definition for risk assessment: Cyflufenamid.	RMS: see RMS response at 3 (5). Addressed	Refer to open point in 3(5)

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(9)	Vol.3, B.7.3 Definition of the residue (pg246)	EFSA: EFSA does not agree with the RMSs' conclusion that residue definition for animal products is not needed. Cyflufenamid is considered fat-soluble (log pow 4.7) and possibly has the potential to accumulate upon longer exposure than covered by the metabolism study. 149-F1 and 149-F6 are of higher	RMS: see RMS responses at 3 (5) and 3 (7). The EFSA concern is appreciated for compounds of potential fat-solubility however in this case it is considered that residues are generally too low in an appropriately conducted goat metabolism study in which a plateau was appeared to have been reached quickly (by day two) to necessitate further study. It is noted that DE also agree that there is not a need to	Refer to open point in 3(5)

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)
		acute toxicity than parent and not fully tested. Thus, they might be also considered in a risk assessment residue definition. For risk assessment purposes a residue definition for livestock should be proposed.	consider residues further in risk assessment terms for animal products (see the DE comment at point 3 (5)). Addressed.	
3(10)	Vol. 3, B.7.3, Definition of the residue (pg 246)	NL: RMS does not propose a residue definition for animal products. NL disagrees and believes it is necessary to propose a residue definition for animal products for risk assessment, i.e. parent cyflufenamid. It is not necessary to propose a residue definition for animal products for monitoring.	RMS: see RMS responses at 3 (5), 3 (7) and 3 (9) which we think address this NL comment. The NL comment seems contradictory; to agree that further feeding studies are not necessary as no significant residues are expected, and then alternatively to propose that some further form of evaluation and risk assessment for residues in animal products is needed. Addressed.	Refer to open point in 3(5)
3(11)	Vol. 1, Level 2, 2.4.1, Definition of the residues (pg 17)	NL: See also comment (1). A residue definition for animal products for risk assessment should be proposed, i.e. parent cyflufenamid. It is not necessary to propose a residue definition for animal products for monitoring.	RMS: see RMS responses at 3 (5), 3 (7), 3 (9) and 3 (10). Addressed	Refer to open point in 3(5)

Use pattern, critical GAP, residues trials (B.7.4 to B.7.6)				
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)
3(12)	Vol.3., B.7.5 Identification of critical GAPs (pg247)	EFSA: The range (of 30 days) for the PHI is unclear in terms of what is the critical GAP. The cGAP should be identified as the one with the highest application rate at the latest possible application time and with the shortest PHI.	RMS: For cereals it is considered that at these growth stages, the growth stage should be the indicator for expression of the GAP. The number of days is expected to only be reliable in terms of Good Agricultural Practice if it is a relatively short number of days (practical for the farmer to count the days). The applicant included the number of days in the GAP table, probably as a guide as to the expected number of days that correlate with this growth stage. Therefore the GAP latest timing of application for wheat and barley is GS 59 (and this is reflected in the trials applicable to GAP). Addressed	Addressed The cGAP identified by RMS in column 3 is agreed. However, for the sake of transparency the cGAP should be reported in the respective paragraph B.7.5 'Identification of critical GAP' in the DAR. To be transferred into an addendum/ corrigendum as appropriate

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(13)	Vol.3, B.7.16.2.1, pg 267, and Vol. 1, 2.4.2, pg 20,and list of endpoints, pg 73, Long term dietary intakes	DE: Comment: The German proposal for the ADI differs from the RMS proposal (see above). Therefore, the NTMDI calculations were reevaluated for both possibilities with German consumption data. With regard to an ADI of 0.04 mg/kg bw (German proposal) the NTMDI accounts for 1.8 % of the ADI. Based on an ADI of 0.017 mg/kg bw (RMS proposal) the NTMDI	RMS: With regard to the above comments on toxicological reference values (see section 2 of the reporting table on toxicology), it is understood that there will be discussion of the ADI. Should there be an agreed change to the value, then the risk assessment calculations will need to be updated. No long term consumer exposure concerns are anticipated.	Addressed subject to confirmation of the ADI Should there be a change to the ADI upon toxicology experts' discussion, then the risk assessment will need to be updated.

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)
		accounts for 4.3 % of the ADI. However, with both ADI values a chronic risk can be excluded.	Addressed (subject to confirmation of the ADI).	
3(14)	Vol.3, B.7.16.2.2, pg 270, and Vol. 1, 2.4.2, pg 20 and list of endpoints, pg 73, Short term intakes	DE: Comment: In Germany, a higher ARfD of 0.1 mg/kg bw/d was established (see above). Therefore the NESTI calculations were re-evaluated for both possibilities with German consumption data. With the German proposal of the ArfD (0.1 mg/kg bw) as well as with the RMS proposal of the ArfD (0.05 mg/kg bw), the NESTI values for cereals are less than 1 % of the ArfD. No acute risk will be expected with both ArfD values.	RMS: With regard to the above comments on toxicological reference values (see section 2 of the reporting table on toxicology), it is understood that there will be discussion of the ARfD. Should there be an agreed change to the value, then the risk assessment calculations will need to be updated. No short term consumer exposure concerns are anticipated. Point Addressed (subject to confirmation of the ARfD).	Addressed subject to confirmation of the ARfD Should there be a change to the ARfD upon toxicology experts' discussion, then the risk assessment will need to be updated.

Comments received on reporting table, section Residues (B.7)			
Reference to reporting table	MS / Notifier	Comment	EFSA response
Further comment to Vol. 3, B.5.3.2 Residues in water	DE	The proposed enforcement method for drinking water is not valid for confirmation of positive findings. The use of m/z 188, 294 and 321 was validated for concentrations 100 times higher than 0,1 µg/l only. For filling this data gap notifier shall provide the study of Brewin, S. A. " NF-149 and Metabolites: Development and validation of methodology for the determination of residues in soils from three sites in Southern France, Northern France and Germany, and for the determination of residues in soil and water from a site in the UK", Report No. NOD 137/002147, Report No. RD-II02006.	Comment transferred to section 1 of the reporting table. See comment 1 (37) (Column 2).
Answer to the DE	RMS	The RMS agrees that the confirmation method was validated quantitatively at 100 times greater than the LOQ of the enforcement method, but considers that the requirements of the confirmatory method as	Answer to the comment

Comments received on reporting table, section Residues (B.7)			
Reference to reporting table	MS / Notifier	Comment	EFSA response
comment		defined in SANCO/3030/99 i.e. to demonstrate specificity, have been met and no further data are required. Addressed. The study of Brewin, S.A., 2000, NOD 137/002147, report no.RD-II2006 was submitted in the original dossier to support pre-registration studies, not as an enforcement method. The method determines residues of cyflufenamid and metabolites in leachate water by LC-MS at levels down to 0.05 µg/l.	transferred to section 1 of the reporting table. See comment 1 (37) (Column 3).

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, List of end points, Rate of degradation	EFSA: The number of soils tested to derive the DT_{50} values for the metabolite 149-F is three.	RMS: The Endpoints have been updated. Addressed.	Addressed
4(2)	Vol. 1, List of end points, Field studies ??	EFSA: For reason of completeness it would be better to specify that no DT50 values for the metabolites 149-F, 149-F1, 149-F6 and 149-F11 are available because no quantifiable residues were detected in the field trials.	RMS: The Endpoints have been updated. Addressed.	Addressed
4(3)	Vol. 3, B.8.1.1.1 Route of degradation I soil, pg 281	EFSA: The argument provided on the natural occurrence of phenyl acetic acid (PAA) in soil seems to be plausible. However, further details on the monitoring study performed in Japan should be provided to support the reported natural background concentrations in soil.	RMS: The Applicant provided limited details of the Japanese monitoring study. The test soil was reported to be a heavy clay soil and analysis was via GC/MS. The Applicant could be asked to provide further details to support the reasoned case. Data requirement	Data requirement Applicant to provide further details on the monitoring study on phenyl acetic acid (PAA) in soil performed in Japan, to support the reported natural background concentrations in soil. In the comments received on the reporting table, the applicant stated that the study has been submitted to RMS on 6 June 2007.

<table>
<tr><th colspan="5">Route and rate of degradation in soil (B.8.1)</th></tr>
<tr><td>No.</td><td>Column 1
Reference to DAR (vol., point, page)</td><td>Column 2
Comments from Member States or applicant</td><td>Column 3
Evaluation by (RMS) rapporteur and
- if available – (Co-RMS) Co-rapporteur</td><td>Column 4
Data requirement or Open point (if data point not addressed or fulfilled)</td></tr>
<tr><td>4(4)</td><td>Vol. 3, B.8.1.1.3 Route and rate of degradation in soil – summary and assessment, pg 304</td><td>EFSA: It is not clear how the mean rate constant k was derived for the parent and if it corresponds to the geometric or the arithmetic mean.</td><td>RMS: The RMS can confirm that the value of 0.02873 d^{-1} is the arithmetic mean rate constant for the parent from 6 soils tested at 20°C.

Details of the calculation are shown below:-
<table>
<tr><td>Soil</td><td>k</td><td>dt50</td></tr>
<tr><td>arrow</td><td>0.01711</td><td>40.5</td></tr>
<tr><td>evesham</td><td>0.03371</td><td>20.6</td></tr>
<tr><td>bromsgrove</td><td>0.07742</td><td>8.95</td></tr>
<tr><td>speyer</td><td>0.00575</td><td>121</td></tr>
<tr><td>abington</td><td>0.03670</td><td>18.9</td></tr>
<tr><td>terling</td><td>0.00168</td><td>412</td></tr>
<tr><td>Arithmetic mean</td><td>0.02873</td><td>-</td></tr>
</table>
Addressed.</td><td>Open point
RMS to add in the LoEP the mean/median value for parent DT50lab and for metabolites (as they were used for PECsoil calculations) and to specify that the reported mean values for metabolites (normalised for FOCUS modelling) refer to arithmetic mean.</td></tr>
</table>

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. 3 B.8.1.3 Fieldstudies	NL: Degradation seems to be dependent on the organic matter content. At high om% the degradation is much slower. In field studies only soils with low om % are tested.	RMS: The RMS agrees with the observation that the slowest dissipation occurred in the two soils with the highest %OM content (e.g. SFO DT50 of 121 and 412d in the Speyer 2.2 and Terling soils with %OC of 2.8 and 3.1% respectively). In general there was noted to be a relatively wide range in the available DT50 values for the parent (i.e. from 7.1 to 412 d) which was somewhat unusual. It is possible that the degradation is partly influenced by the relatively strong sorption, which was also noted to correlate well with soil organic content (i.e. strongest sorption in soils with highest %OC, which may reduce the fraction available for degradation). With regard choice of field trial sites, the RMS accepted that a reasonable range of locations had been selected, covering both NEU and SEU and a range of soil characteristics and therefore accepted the data submitted as being sufficient. The Applicant could be asked to provide further information to support the choice of field trial sites, specifically with regard %OM content. Data requirement	Data requirement Applicant to provide further information to support the choice of field trial sites, specifically with regard %OC content, to cover the wide range of European conditions. See also comments in 4(7) and 4(10). In the comments received on the reporting table, the applicant stated that the study has been submitted to RMS on 6 June 2007.

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(6)	Vol. 3, B.8.2, pg 307, Soil adsorption and desorption Vol. 1, List of endpoints, ads/des box Vol. 1, List of endpoints, PECgw box	EFSA: Please, specify the unit of measure of Koc values.	RMS: The units of Koc should read ml/g. The Endpoints have been updated. Addressed.	Addressed
4(7)	Vol 1, level 2 list of endpoints Box Laboratory studies	NL: Presented DT90 values are calculated from the presented DT50 using the standard value of 3.3. Because the degradation pattern is not first order this is an under estimation of the DT90. The mean DT90 is > 1 year based on the DT90 values calculated with the 2 compartment model. For assessing against trigger values best fit values must be used. This is important for the ecotox section. Further it should be discussed if an accumulation study for soils with a high om% is necessary.	RMS: The DT50 and DT90 values presented in the Endpoints are those derived according to simple first order kinetics only. The simple first order fits only are presented since on the basis of the r^2 values >0.7 the RMS considered these fits acceptable. It should be noted that the DAR was prepared during 2003, before the detailed guidance in the FOCUS degradation kinetics report became available. Hence the RMS followed the relatively simple guidance available at the time of evaluation present in the "Guidance Document on Persistence in Soil", EC 9188/VI/rev.8. On the basis of the field studies the DT90 is clearly less than 1 year. However see also response to point 4(5) above. Addressed (and refer to 4(5) for possible related data requirement).	Addressed. See data requirement in comment 4(5).

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(8)	Vol. 3, B.8.3 PECsoil, pg 316	EFSA: The reference of the original study on PECsoil calculations provided by the applicant (and used in the assessment) is not quoted. Moreover, it is not clear which DT50 values were used to calculate PECsoil for the metabolites.	RMS: The RMS can confirm that calculation of PECsoil provided by the Applicant was presented in their MIII summary document only, and therefore no specific reference to this is included in the DAR. The maximum initial metabolite PECsoil values were calculated based on a total dose of the parent of 20g a.s./ha (taken as the sum of 12.5 and 7.5 g a.s./ha following application of appropriate crop interceptions for each application of 25 g a.s./ha) and were therefore effectively independent of the DT50 assumed. The point and TWA values over time were calculated based on arithmetic mean rate constants from laboratory studies and the actual DT50 values used are provided in the LOEP. Risk assessments are based on the maximum initial metabolite PECsoil values and therefore the DT50 used is of less importance. Addressed.	Addressed. See open point in comment 4(4).
4(9)	Vol. 3, B.8.3 PECsoil, pg 317	EFSA: PECsoil are calculated considering a 50% interception by crop. This is already a refinement step, and PECs in soil should initially be calculated with no interception.	RMS: The RMS does not consider this is consistent with the data requirements under Commission Directive 95/36 which clearly states that 50% interception should be assumed when ground cover is present at the time of application. The Applicant has followed the more modern assessment methods using the crop interception tables available in the FOCUS groundwater guidance and the RMS considered this approach acceptable.	Addressed

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)
			Addressed.	
4(10)	Vol.1, 2.5.2.4 (pg 26); Vol. 3 B.8.3 PEC s	NL: For the PEC s calculation the highest available field DT50 of 91 days is used. It is stated that this is a representative worst case value. Because at high om% the degradation is much slower and in field studies only soils with low om % are tested this is questionable.	RMS: See response to 4(5) above.	See data requirement in comment 4(5).

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(11)	Vol. 1, List of end points, PECgw	EFSA: Please consider providing details (dose and time of application) on the modelling for metabolites as independent compounds.	RMS: The dose and timing of application have been added to the Endpoints. Addressed.	Addressed
4(12)	Vol. 3, B.8.6.1 PECgw, reference, pg 327	EFSA: The reference of the original study on PECgw calculations provided by the applicant (and used in the assessment) is not quoted.	RMS: The RMS can confirm that calculation of PECgroundwater provided by the Applicant was presented in their MIII summary document only, and therefore no specific reference to this is included in the DAR. Addressed	Data requirement Applicant to provide the original study on PEC groundwater calculations. In the comments received on the reporting table, the applicant stated that the information on the calculation of PECgw has been submitted to RMS on 6 June 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(13)	Vol. 3, B.8.6.1 PECgw, input parameters, pg 327	EFSA: According to FOCUS, the geometric mean of the DT50field values (25.3 days for the cyflufenamid) should be used in GW modelling.	RMS: The DAR was prepared during 2003, prior to the release of the FOCUS degradation kinetics guidance document. The DAR was prepared using the best available guidance at the time. Given the relatively high Koc and large margin of safety on the parent PECgw, the RMS does not consider that a revised FOCUSgw modelling assessment using a marginally longer DT50 (i.e. 25.3 d versus the current 19.4 d used in the DAR) would alter the conclusions of the DAR with respect groundwater leaching potential of cyflufenamid. Addressed	Addressed
4(14)	Vol. 3, B.8.6.1 PECgw, modelling, pg 327	EFSA: Further explanations to defend the approach used to model the four metabolites as independent compounds (single application on soil surface on the date of the second application of parent compound) should be provided.	RMS: The degradation pathway for cyflufenamid was relatively complex and it was not possible to produce a kinetic analysis of the formation fractions of metabolites in parent degradation studies. The four soil metabolites were thus simulated as independent compounds. Inputs to soil have been calculated assuming an instantaneous input of parent compound at 20.0 g a.s./ha (the sum of 12.5 and 7.5 g a.s./ha) and considering the maximum accumulation of each metabolite in laboratory degradation studies and the ratio of molecular weights of parent and metabolite (the Endpoints have been updated with this information). This was considered to be an appropriate approach in the absence of further details on formation fraction etc. Based on a	Open point: MS to discuss the suitability of the approach used to model the metabolites for groundwater contamination in a meeting of experts. EFSA note: the direct application of metabolites instead of using sequential degradation in the model would result in a best case as the amount of the leaching of metabolite during its formation from the parent is excluded in the modelling. Therefore this approach is not recommended.

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)
			simple consideration of fate properties (e.g. DT50 and Koc) it is clear that 149-F1 and 149-F6 are the metabolites of potential concern in groundwater. Both these are regarded as non-relevant according to SANCO/221/2000-rev.10, February, 2003 and therefore the assessment is considered acceptable. Addressed.	
4(15)	Vol. 3, B.8.6, PEC_{SW}, PEC_{SED} (pg 327)	AT: We have FOCUS SW/SED STEP 1 – 4. So, why not use them?	RMS: The DAR was prepared during 2003 prior to the release of the FOCUS surface water models and tools. The DAR was prepared using the best available guidance at the time of application. The final conclusions of the EU peer review process could highlight that MS will need to consider the potential for surface water contamination via runoff and drainflow during National Authorisations (for consistency with other substances assessed prior to implementation of FOCUSsw). Addressed.	Addressed.
4(16)	Vol. 3, Point B.8.6, PECs in surface water and sediment (pg 327)	DE: PECs in surface water were calculated based on an outdated Guidance Document and not according to FOCUS (2003). It is suggested that FOCUS (2003) PEC calculations are done and filed by the notifier.	RMS: See response to 4(15) above.	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)
4(17)	Vol.1, 2.5.2 (pg 23); Vol. 3 B.8.6 PEC gw	NL: According to FOCUS a mean DT50 should be used and not a DT50 calculated from a mean rate constant. Mean DT50 field based on the available data is 36 days.	RMS: See response to 4(13) above.	Open point MS to discuss the appropriate DT50 value to be used in FOCUSgw modelling in a meeting of experts.

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(18)	Vol. 1, List of end points, Table of intended uses (pg 52)	EFSA: It is noted that in the whole assessment in the fate section, the application of cyflufenamid is considered to be in late May and June. This is inconsistent with the indication for a "spring application" as reported in the GAP table. Please consider also adding the minimum interval between applications of 21/28 days since the exposure assessment (PECgw) for spring/winter cereals was based on this value.	RMS: None of the exposure assessments have been based specifically on applications in May/June. Rather the assessments are based on 2 applications being made between BBCH 30-59 at 28 d intervals. In the UK, BBCH 30 in winter cereals would always be in the Spring, and could be as early as mid-April. Again in the UK, BBCH 59 would likely be reached by mid-June. The RMS considers that the current Table of Intended Uses sufficiently represents the timing of application currently assessed in the fate section. The Endpoints have been updated to include a minimum 28d application interval, and this is line with the GAP used in the residues and ecotoxicology risk assessments. Addressed.	Open point RMS to provide explanations on the inconsistency between the timing of application as indicated in the GAP table and the actual dates of application used in the assessment. EFSA note: it is noted that in all field trials cyflufenamid was applied in late May or middle June. In addition, in FOCUS GW the crop interception factors were calculated based on applications to cereals at GS 20-39 and GS 40-89 (it was not possible to check the actual dates of application used in the modelling because the original report on FOCUS PECgw is not available).

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(19)	Vol. 3, General	EFSA: A clear statement if studies are considered acceptable by RMS should be included in the DAR.	RMS: The RMS accepts that this point is not clear. However the RMS can confirm that all studies presented in the DAR were considered acceptable and relied upon. Addressed.	Addressed.
4(20)	Vol. 3, B.8.10 References relied on, pg 337	EFSA: The reference Brewin (2002) on p.300 is not reported in the list. Please clarify.	RMS: The correct reference is below:- Brewin, S.A. (2000). Development and validation of methodology for the determination of residues in soils from three sites in Southern France, Northern France and Germany, and for the determination of residues in soil and water from a site in the United Kingdom. Huntingdon Life Sciences Ltd., Laboratory no. NOD 137/002147. Nippon Soda Company Ltd., Report no. RD-II02006, GLP, unpublished. The references relied on list will be updated. Open point	Open point RMS to update the list of references relied on with respect the reference Brewin (2002).
4(21)	Vol. 3, B.8.10 References relied on, pg 337	EFSA: A cross reference between the phys-chem and the fate section for the studies by Yamasaki (1999), Aikens (2001) and Aikens & Millais (2002) should be made in the List of References relied on.	RMS: The references relied on list will be updated. Open point	Open point RMS to update the list of references relied on with a cross reference between the phys-chem and the fate section for the studies by Yamasaki (1999), Aikens (2001) and Aikens & Millais (2002)

Comments received on reporting table, section Environmental fate and behaviour (B.8)			
Reference to reporting table	MS / Notifier	Comment	EFSA response
4(3)	NOT	A report (number RD-01179) on the determination of the levels of phenylacetic acid (PAA) in Japanese soil has been submitted to RMS on 6 June 2007. It shows that the PAA content was 0.076 mg/kg of soil which is 1.6 times higher than the maximum theoretical residue that could be formed from cyflufenamid (NF-149).	Noted and date of submission included in the reporting table
4(5)	NOT	The justification that the maximum organic matter content in typical cereal growing areas in the EU is 3-5% has been provided to the RMS on 6 June 2007.	Noted and date of submission included in the reporting table
4(12)	NOT	A separate study report on PECgw calculations is not available. This is not unusual as separate reports are not normally produced for other risk assessments (e.g. for assessing risks to avian, aquatic and other terrestrial vertebrates) as they are derived from information contained in the dossier. Information on the calculation of PECgw was presented in the Tier II summary in Annex III, Point 9.2.1, Section 5 of the EU dossier and was acceptable to the RMS. This information has been provided to RMS on 6 June 2007.	Noted and date of submission included in the reporting table
4(14)	NOT	Justification that there is negligible potential for cyflufenamid and its metabolites to leach to groundwater at concentrations of 0.1 µg/l and above has been provided to RMS on 6 June 2007. Evidence for this is the findings in a higher tier leaching study.	Open point is set.

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. 3, B.9.1.3, Long term toxicity to birds, pg 345	EFSA: It is noted that at 1000 ppm the number of 14-day old survivors was 29% less than in the control group. This effect was statistically not significant. Was this effect also within the historical control range?	RMS: The nos. of 14d old hatchling survivors /female at all treatment doses were within the historical range (35.3 - 48.3) from 10 previous studies. Addressed	Addressed
5(2)	Vol. 3, B.9.1.4, pg 347, Risk to birds and B.9.3.2, pg 376, Risk to mammals	EFSA: How was the MAF of 1.1 for the acute risk assessment calculated?	RMS: The GAP proposes a max of 2 applications without specifying a specific spray interval period. The RMS considers an appropriate spray interval to be 28d (see DAR B.9.1.4 for refs.). SANCO4145/2000 (Table 3) does not provide a MAF value for a spray interval period of 28d. However, a MAF_a value with a 28d spray interval for short grass was derived by formula. Addressed	Addressed
5(3)	Vol. 3, B.9.1.4, pg 347, Risk to birds and B.9.3.2 pg 376, Risk to mammals	EFSA: Preferably also the risk to birds and mammals from consumption of contaminated drinking water is discussed.	RMS: Birds feeding on insect and leaf diets are not expected to have a high supplementary drinking water requirement. Furthermore, from the proposed uses, due to interception and leaf coverage spray accumulation in leaf axils and on soil surface is expected to be negligible. Nevertheless, TER_as derived according to SANCO 4145/2000 for the indicator birds (large herbivore & insectivore) and mammals (medium herbivore & insectivore) were 1948, 297, 1397 and 1275, respectively, confirming low risk. Inserted into Endpoints.	Addressed. However, for transparency reasons please indicate in the list of endpoints how these values were derived since the calculations are not presented in the DAR (e.g. refer to the allometric equation in SANCO/4145/2000.

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)
			Addressed	
5(4)	Vol. 1, List of endpoints, Toxicity/exposure ratios for terrestrial vertebrates, p. 63	EFSA: Preferably also the TER-values for earthworm- and fish-eating birds are included in the list of endpoints.	RMS: The Endpoints have been amended. Addressed	Addressed. The list of endpoints has been updated.
5(5)	Vol. 3, B.9.3.1, Toxicity to mammals, pg 376	EFSA: The NOEC for mammals was set at 75 mg/kg bw based on the study by Patten (2000a, b and c). Meanwhile the opinion of the PPR Panel on the setting of the NOEC for mammals was published. The Panel recommends taking effects on number aborting from the developmental study into account. Total litter resorption was observed at 60 mg/kg bw during the developmental study on rabbits by Patten (2000f, g and h). The resulting NOEC from this study is 10 mg a.s./kg bw/day. Please verify.	RMS - Total litter resorption was considered to be a spontaneous treatment-unrelated incident. Abortions at the highest dose level (300 mg a.s./kg bw/d) were a consequence of severe maternal toxicity. The NOEC selected was considered the most appropriate endpoint reflecting reproductive effects. Addressed.	Open point: The toxicity endpoint for the long-term risk assessment for mammals to be discussed in an experts' meeting.

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(6)	Vol. 3, B.9.2.3.2, Long term toxicity to *D. magna* pg 361	EFSA: The reproductive NOEC for *D. magna* was set at 0.246 mg a.s./L as there was no statistical difference in the total number of neonates when compared to the solvent control. This is surprising as at that test concentration 70% adult mortality was observed.	RMS: The repro NOEC was based on mean no. neonates/adult surviving at 21d. For the 0.246 mg a.s./L group at d21, nos. of total neonates/surviving adult were similar to those of solvent control and hence a statistical difference in mean nos./adult was not apparent. It should also be noted that NOEC for *Daphnia* parental survival (0.0406 mg a.s./L) was also used in the risk assessment. See also 5(9). Addressed	Addressed
5(7)	Vol. 3, 9.2.4.4, Risk to aquatic organisms, pg 374	EFSA: The highest concentration in groundwater for the metabolite 149-F6 is for an application in winter cereals in Seville (PECgw = 0.527 µg 149-F6/L) instead of spring cereals in Jokioinen (PECgw = 0.397 µg 147-F6/L).	RMS: Agree. Revised TERs for fish, Daphnia and algae for 149-F6 are >186907, >195446 and 191651, respectively, LOEPs have been amended. Addressed.	Addressed No amendments of the list of endpoints could be seen. However, the TERs for this metabolite with respect to spray drift, drainage and run-off are included and are far above the trigger. No further action needed.
5(8)	Vol. 1, List of endpoints, Toxicity data for aquatic species, p. 63-64	EFSA: Preferably both the biomass as the growth rate EC_{50} for algae are included in the list of endpoints even though these values are for some of the tested substances equal. Furthermore a small typo was noted in the TER-value for fish for the metabolite 149-F from the drainflow route. Instead of 57213 this value should read 57123.	RMS: Both comments acknowledged and LOEPs amended. Addressed.	Addressed The list of endpoints has been updated.

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(9)	Vol. 3, B.9.2.4.1 Acute risk aquatic organisms (pg 369)	NL: The 48h LC50 for *Daphnia magna* is > 1.73 mg a.s./L for the active substance. But the chronic study with *Daphnia magna* showed a LC50-value of 0.157 mg a.s./L. How can this difference be explained? Maybe there is a delayed effect on mortality, which was not shown in the acute study because of the short test period. So the incipient LC50 seems to be much lower than the 48 h LC50-value. This should be taken into account in the risk assessment.	RMS: The effects seen in 21d LC50 may be attributable to prolonged sublethal effects (adult size and reproductive ability were affected after at higher doses 0.246 and 0.575 mg a.s./L) and most mortality occurred after 18d. The chronic risk assessment takes account of such effects by using the NOEC for parent survival at 0.0406 mg a.s./L. It should also be noted that the 48hLC50 of 1.73 mg a.s./L may be affected by solubility of the a.s. and hence for acute risk assessment the acute 48h LC50 (0.491 mg a.s./L) from the EW product is preferred. See also 5(6). Addressed	Addressed
5(10)	Vol. 3, B.9.2.4.1 Acute risk aquatic organisms (pg 369)	NL: Why the concentrations in surface water are not calculated according to FOCUS?	RMS: Addressed at point 4(15).	Addressed

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(11)	Vol. 1, List of endpoints, Toxicity data for earthworms, p. 67	EFSA: It is noted that the given acute endpoints for earthworms from studies with the a.s., 149-F and 149-F11 in the list of endpoints are not corrected for the Log Pow. Also the NOEC from the study with	RMS: Agreed. The Endpoints have been amended. Addressed	Open point: RMS to clarify whether the LC_{50} for earthworms reported as 25 mg a.s./kg based on 'NF-149 EW' has been corrected for organic content in soil.

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)
		the formulation is not corrected in the list of endpoints. Please give the corrected values and indicate clearly all corrected values with a footnote or in subscript.		The Notifier has indicated that a clarification will be provided by 6 June.
5(12)	Vol. 3, B.9.6.2.3, Long term toxicity to earthworms, pg 394	EFSA: Although this will not change the outcome of the assessment, for a chronic earthworm study to be valid the coefficient of variation of the control group should not exceed 30% (and not 50% as stated) according to OECD202. The coefficient of variation in the other test groups and the difference with the control should not be taken into account when deciding on the validity of a study.	RMS: Typo. Agree the coefficient of variation for the number of offspring in the control group was 28.15%, i.e. <30%. Addressed	Addressed. RMS to consider in a corrigendum
5(13)	Vol. 1, List of endpoints, Toxicity data for soil micro-organisms, p. 67	EFSA: Preferably the tested dose rates in the study on soil micro-organisms with the a.s. are given as mg/kg soil instead of mg/5 kg soil to facilitate comparison to the PECsoil values.	RMS: Agree. The Endpoints have been amended. Addressed	Addressed The list of endpoints has been updated.

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(14)	Vol. 3, B.9.8.1.3, Effects on soil micro-organisms, pg 404	EFSA: Given the $DT_{90field}$ for cyflufenamid, a study on soil micro-organisms with the lead formulation should be envisaged.	RMS disagrees: Soil microbial activity deviated <25% control activity in soil treated with cyflufenamid at approximately 2.5 and 12.5x the maximum predicted soil concentration. According to SANCO 10329/2002, this is sufficient indication of low risk from cyflufenamid to soil microbial processes following the proposed use on cereals. Since formulation integrity will not be significantly maintained after contact with soil and predicted soil concentrations are based on a.s. properties the relevance and extra value of undertaking another study using the formulation is considered questionable and hence not justifiable. Addressed.	We agree. Addressed.
5(15)	Vol. 3, B.9.8.1.3, Effects on soil micro-organisms, pg 403	EFSA: According to OECD 216 and 217, a soil micro-organisms test should run for at least 28 days. As the study with the parent only ran for 28 days, the metabolites will never have been tested long enough. Furthermore the peak for 149-F only appears after 44 days. Therefore the need for a study on soil microbial mineralisation and nitrogen transformation with the metabolites 149-F and 149-F11 should be reconsidered.	RMS - Disagrees. It has been established (see Env fate endpoints) using DT50s for metabolites 149-F and 149-F11 of 9.1d and 2.5d, respectively, that PECsoil concentration will be ≤ 10% maximum initial concentration within 28d. Thus it can be assumed that there will have been significant exposure to these metabolites in soil microbial studies using parent and the absence of >25% effect over 28d is sufficient to establish low risk. Addressed	Data requirement: Applicant to address the risk to soil micro-organisms from the metabolites. The statement in column 3 does not address the concern for 149-F. The DT_{50} of 9.1 days might be correct but it takes 44 days for the peak to be reached. The Notifier will provide further justification to RMS (UK PSD) on 6 June 2007.

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(16)	Vol. 3, B.9.7 Other soil non-target macro-organisms (pg 398)	AT: In our opinion litter-bag studies with the metabolites 149-F1 and 149-F6 are considered necessary as their DT90-values are above the relevant trigger of 365 days.	RMS - 149-F1 and 149-F6 are considered to have low biological activity compared to parent (see 5(19)). In addition both metabolites were not acutely or chronically toxic to earthworms, Folsomia and soil microbial processes and present a low risk at the predicted exposure levels in soil. Overall , the evidence was considered sufficient to indicate a low risk to soil organisms and soil processes. Addressed	Addressed.
5(17)	Vol. 3, B.9.7.2, Risk assessment (soil non-target macro-organisms) (pg 400)	DE: The handling of the effects observed in the Collembola reproduction test with the formulated product is not supported. If there are significant effects at the lowest concentration this value must be used for ERA. The lack of a dose-response relationship could have been checked in a second test. Refinement steps are of course also possible, e.g. performance of a litterbag study. Just to select a NOEC is surely not sufficient.	RMS - The 28d Folsomia study submitted using 'NF-149 EW' was regarded by the RMS as supplementary data only. The RMS agrees that the poor dose-effect relationships make establishment of endpoints unreliable. Nevertheless, an estimated LC50 of 1.26 mg a.s./kg soil and <50% effects on reproduction at 3.55 mg a.s./kg soil may provide supporting evidence of likely absence of significant lasting effects on Folsomia at the max PECsoil of 0.0235 mg a.s./kg. Furthermore, since cyflufenamid has a soil DT90 <365d, according to SANCO 109329/2002, <25% effect on soil microorganisms after 28d, a worm TERlt >5 and HQs <2 for the standard NTAs are sufficient without the need for further testing to establish a low risk to soil organisms and processes. Addressed	Open point: The reproduction test with Collembola to be discussed in an experts' meeting. There seems to be no formal data requirement for a Collembola study. However, since the study is available the validity and results should be discussed. See also 5(18)

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(18)	Vol. 3, B.9.7.1.3 Plant protection product (pg 399)	NL: The NOEC for reproduction (< 0.00355 mg a.s./kg dry soil) regarding *Folsomia candida* is much lower than the NOEC for survival (0.0355 mg a.s./kg dry soil. Why the NOEC for reproduction has not been taken as the relevant value for risk assessment?	RMS: Addressed at 5(17).	See 5(17)

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(19)	Vol. 3, B.9.9.2, Risk to non-target fauna and flora Pg 406	EFSA: For reasons of transparency the biological activity of the groundwater metabolites 149-F1 and 149-F6 should be assessed as foreseen in the Guidance Document on the Assessment of the Relevance of Metabolites in the Groundwater of Substances Regulated Under Council Directive 91/414/EEC (SANCO/221/2000).	RMS - 149-F1 and 149-F6 are tertiary and quarternary metabolite fragments of cyflufenamid containing the fluorinated phenyl moiety. It would be anticipated that degradation of the toxophore would result in significant loss of biological activity. This is substantiated by both metabolites not expressing any herbicidal, insecticidal and fungicidal activity, the latter including fungal species susceptible to parent. Furthermore, the metabolites were much less toxic to aquatic organisms than parent and were of overall low toxicity to soil organisms and microbial processes. Hence it can be concluded that metabolites 149-F1 and 149-F6 will likely pose a low ecotoxicological risk. Addressed.	Open point: RMS to give the reference to the studies on which the statement "Cyflufenamid and its metabolites showed no fungicidal activity to non-crop plants as this was specific to cereals and powdery mildew. In addition, neither the parent or its metabolites showed any herbicidal or insecticidal activity" as given in B.9.11was based on.

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(20)	Vol. 3, B.9.9, Effects on other non-target organisms (flora and fauna) believed to be at risk (pg 405)	DE: The statement of the notifier that there are no effects on plants is not supported by data. In addition, the SANCO requirement that at least 6 species have to be used was not fulfilled (only 4). Other tests in which detached and dried leaves were used are not suitable for the evaluation of effects on plants.	RMS - Cyflufenamid demonstrates very specific fungicidal activity largely confined to powdery mildew *Erysiphe graminis* on cereals, fungicidal activity to other common crop fungal species was shown to be absent in tests, which, for grey mould included flower spore inoculation on detached leaves. Cyflufenamid was also shown not to exhibit insecticidal/acaricidal activity in tests on common species. In addition cyflufenamid showed no herbicidal activity to four plant species, negligible influence on rotational crops and phytotoxic, quality and yield effects on treated cereal crops were absent in the field. Together, these data indicate that cyflufenamid has a very specific and narrow spectrum of biological activity and will have minimal impact on non-target plants. The RMS considers the evidence is sufficient to conclude that there is a low risk to non-target plants from cyflufenamid without the need for further data. Addressed	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(21)	Vol. 3, B.9.12, List of references relied upon, p. 409	EFSA: It is not quite clear from the discussion on p. 368 of Vol. 3 if the acute toxicity studies on fish with the a.s. cyflufenamid are considered valid or not. If not, these studies should not be included in the list of references relied upon.	RMS: The studies were considered valid and are relied on to select the formulation endpoint as most appropriate for use in the aquatic risk assessment based on solubility considerations. Addressed.	Addressed
5(22)	Vol. 3, B.9.12, List of references relied upon, p. 414-415	EFSA: There are two position papers by Kawai (2002a and b) for which it is not clear if they were relied upon in the DAR. If not, they should not be included in this list.	RMS: Agree. These two papers were not relied in the ecotox section and should be deleted. The references relied on list will be updated. Open point.	Open point: RMS to delete the two position papers by Kawai (2002a and b) from the reference list.

Comments received on reporting table, section Ecotoxicology (B.9)			
Reference to reporting table	MS / Notifier	Comment	EFSA response
5(11)	NOT	The LC_{50} value of NF-149 EW to earthworms presented in the study report and in the EU dossier was not corrected for the organic content of the soil. The reason for this and the LC_{50} value corrected for this (>500 ppm) has been provided to RMS on 6 June 2007	Noted for the reporting table
5(15)	NOT	The worst case maximum PECsoil for the metabolites (6.6 µg/kg) is more than 40-fold below the applied rate of 294 µg/kg of soil of cyflufenamid which had no effect on carbon and nitrogen transformations. As cyflufenamid and metabolites 149-F1 and 149-F6 had no effect on soil micro-organisms, no risk to soil micro-organisms is expected from other metabolites (149-F and 149-F11). This is supported by their acute toxicity to soil macro-organisms e.g. earthworms. 149-F was only 4 times more toxic to earthworms than cyflufenamid (LC_{50} 149-F = 279 ppm; cyflufenamid LC_{50} >1000 ppm); 149-F1, 149-F6 and 149-F11 were of similarly low toxicity to earthworms as cyflufenamid. The justification will be provided to RMS (UK PSD) on 6 June	Noted for the reporting table

Comments received on reporting table, section Ecotoxicology (B.9)			
Reference to reporting table	MS / Notifier	Comment	EFSA response
		2007.	