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

TABLE OF CONTENTS



Comments on the Draft Assessment Report on cyflufenamid (NAS)

RMS UK

End of commenting period: 14 August 2006 (MS, NOT)

| Date | Supplier | File |
|---|---|---|
| 31.07.2006 | The Netherlands | 01 cyflufenamid comments NL 2006-07-31.doc |
| 03.08.2006 | Germany | 02 cyflufenamid comments DE 2006-08-03.doc |
| 18.08.2006 | Notifier | 03 cyflufenamid comments NOT 20096-08-14.doc |
| 21.08.2006 | Austria | 04 cyflufenamid comments AT 2006-08-21.doc |
| 22.01.2007 | EFSA | 05 cyflufenamid comments EFSA 2007-01-22.doc |

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

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (1) | Vol 1, 1.3.5, CIPAC number | NL: CIPAC number is 759 for cyflufenamid (source: www.cipac.org). | |
| (2) | Vol 1, LOEP, analytical methods for food/feed of plant origin | NL: Please mention LOQ's, validated analytes and matrices, confirmatory methods and ILV. | |
| (3) | Vol 1, LOEP, analytical methods for soil, water and air | NL: Please mention LOQ's, confirmatory methods, analytes and matrices (surface water, drinking water). | |
| (4) | Vol 3, B.2, physical and chemical properties | NL: Please state for every study whether GLP compliance is met. | |
| (5) | Vol 3, B.2.2.17, persistence of foam | NL: At what concentration was the test performed? | |
| (6) | Vol 3, B.2.2.26, emulsifiability | 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? | |
| (7) | Vol 3, B.2.2.13, relative density | NL: This is not a relative density. At what temperature was the density determined? | |
| (8) | Vol 3, B.2.2.20, dilution stability | NL: Please mention this determination is not a requirement or mention at what concentration the test was performed (0.25% required). | |
| (9) | Vol 3, table B.5.1, LOQ | NL: The footnote makes no sense: there is no LOQ mentioned in the table? | |

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

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (10) | Vol 3, table B.5.2, linearity | 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. | |
| (11) | Vol 3, table B.5.1, LOQ | NL: No LOQ is mentioned in the table. What does the footnote refer to? | |
| (12) | Vol 3, B.5.1.1, technical active substance | NL: The method should be more clearly described, including dilution ratios. With the mentioned data it is impossible to conclude linearity was correctly demonstrated. | |
| (13) | Vol 3, table B.5.3., analytical method (residue) for food/feed of plant origin | 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. | |
| (14) | Vol 3, B.5.2, analytcal 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 according to SANCO/825/00. The submitted method displays unacceptable results (ILV). | |
| (15) | Vol 3, B.5.3.3, residues in air | 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/$m^3$. | |

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

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (16) | Vol 3, B.5, analytical methods | 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. | |
| (17) | Vol 4, C.1.2, 5 batch analysis | 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 [redacted] it might be necessary to include this impurity in the specification. The measurements with values below the LOQ of the method should be mentioned as < LOQ. | Example: [redacted] 0.07% in batch 1, with a LOQ of 0.15%<br>This should be reported as < 0.15%, which may mean the impurity should be included in the specification, because it may be significant (> 0.1%w/w). |
| (18) | Vol 4, C.1.4.1, analytical methods for impurities | 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)). | |

**Classification and labelling (B.4), physical and chemical properties**

No comments.

* When mentioning page numbers of the DAR in your comments, **the page numbers should refer to the pdf-version** (not the WORD-version) of the DAR to ensure consistency among the Member States.

section 2 - Mammalian toxicology (B.6)

## 2. Mammalian toxicology (B.6)

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (1) | Vol. 1, list of end points | NL:<br>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. | |
| (2) | Vol. 3, B.6.10.3, AOEL | NL:<br>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 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. | |

section 2 - Mammalian toxicology (B.6)

**Classification and labelling (B.4), part mammalian toxicology**

No comments.

section 3 - Residues (B.7)

### 3. Residues (B.7)

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (1) | Vol. 3, B.7.3, Definition of the residue | NL: RMS does not propose a residue definition for animal products.<br>NL disagrees and believes it is necessary to propose a residue definition for animal products for risk assessment, i.e. parent cyflufenamid.<br>It is not necessary to propose a residue definition for animal products for monitoring. | According to B.7.16.1 there are significant residues in cattle feed. The next step is to evaluate the level of residues in animal tissues. A residue definition for risk assessment is needed before it can be evaluated whether or not significant residues will occur in edible animal tissues. So a residue definition for animal products for risk assessment should be proposed, i.e. parent cyflufenamid.<br>The goat metabolism study does indeed indicate that no significant residues of parent are expected in animal tissues. So a livestock feeding study is not required, nor the subsequent setting of MRL's. And it is also unnecessary to propose a residue definition for animal products for monitoring. |
| (2) | Vol. 1, Level 2, 2.4.1, Definition of the residues | NL: See also comment (1).<br>A residue definition for animal products for risk assessment should be proposed, i.e. parent cyflufenamid.<br>It is not necessary to propose a residue definition for animal products for monitoring. | |
| (3) | Vol. 1, Level 2, Appendix 3, List of End Points, Metabolism in livestock | NL: See also comment (1).<br>Animal residue definition for monitoring: Not required.<br>Animal residue definition for risk assessment: Cyflufenamid. | |

**4. Environmental fate and behaviour (B.8)**

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (1) | Vol. 3 B.8.1.3 Fieldstudies | 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. | |
| (2) | Vol.1, 2.5.2.4; Vol. 3 B.8.3 PEC s | 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. | |
| (3) | Vol.1, 2.5.2; Vol. 3 B.8.6 PEC gw | 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. | |
| (4) | Vol 1, level 2 list of endpoints | | |
| (5) | Box Laboratory studies | 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. | |

* When mentioning page numbers of the DAR in your comments, **the page numbers should refer to the pdf-version** (not the WORD-version) of the DAR to ensure consistency among the Member States.

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

## 5. Ecotoxicology (B.9)

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (1) | Vol. 3, B.9.2.4.1 Acute risk aquatic organisms | 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. | |
| (2) | Vol. 3, B.9.2.4.1 Acute risk aquatic organisms | NL: Why the concentrations in surface water are not calculated according to FOCUS? | |
| (3) | Vol. 3, B.9.7.1.3 Plant protection product | 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? | |

**6. Mammalian toxicology (B.6)**

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca. 10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (1) | Vol 3, B6.10.1 and Vol. 1, 2.3.2 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. | |
| (2) | Vol 3, B6.10.3 and Vol. 1, 2.3.4 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. This AOEL-S (0.05 mg/kg bw/d) would be 460-fold lower than the NOAEL for brain vacuolisation seen in this study. | |

section 2 - Mammalian toxicology (B.6)

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca. 10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (3) | Vol 3, B6.10.3 and Vol. 1, 2.3.3 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. | |
| (4) | Vol. 3, B.6.11.d) Skin irritancy and Vol. 1, 2.1.4.2 | 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. | |
| (5) | Vol 3, B.6.12 and Vol. 1, 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. | Assessing dermal absorption, the amount of substance found in the skin should be treated as absorbed (guidance document on dermal absorption, SANCO/222/2000 rev. 7). In the in vivo study, the skin depot was considered as absorbed substance. The same should be done in the in vitro study. This would lead to a 1.5- to 5-fold higher absorption of substance by rat skin than by human skin.<br>As a consequence the in vitro-in vivo extrapolation should be re-calculated, leading to 1 or 8 % dermal absorption of the concentrate or the dilution, respectively. |

section 2 - Mammalian toxicology (B.6)

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca. 10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (6) | Vol 3, B.6.14, Exposure data | 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 (5)] and a systemic AOEL of 0.05 mg/kg bw/d [see (2)], the operator, worker and bystander exposure would also be acceptable | |

section 3 – Residue data (B.7)

**7. Residues (B.7)**

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca. 10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (1) | Vol. 3, B.7.3 and Vol. 1, 2.4.1 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 in the goat metabolism study we propose to appoint cyflufenamid as residue definition for animal matrices. | A residue definition for animal matrices should be defined for a complete assessment of cyflufenamid and in view of possible future uses of cyflufenamid, particularly a metabolism study is available. Possible future uses of cyflufenamid might be treatments on cereals with higher application rates or at later growth stages or treatments on other crops fed to animals. |
| (2) | Vol.3, B.7.16.2.1 and Vol. 1, 2.4.2 and list of endpoints, 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.<br>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 accounts for 4.3 % of the ADI.<br>However, with both ADI values a chronic risk can be excluded. | The calculations for the dietary risk assessment are based on new German consumption data for toddlers of 2 to <5 years of age with a mean body weight of 16.15 kg (VELS project; Banasiak, U., Heseker, H., Sieke, C., Sommerfeld, C. and Vohmann, C.: “Estimation of the dietary intake of pesticide residues based on new consumption data for children.”, Bundesgesundheitsbl 1, 2005) |

section 3 – Residue data (B.7)

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca. 10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (3) | Vol.3, B.7.16.2.2 and Vol. 1, 2.4.2 and list of endpoints, 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 reevaluated for both possibilities with German consumption data.<br>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. | |

**8. Environmental fate and behaviour (B.8)**

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (1) | Vol. 3, Point B.8.6, PECs in surface water and sediment | 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. | |

**9. Ecotoxicology (B.9)**

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca. 10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (1) | Vol. 3, B.9.7.2, Risk assessment (soil non-target macro-organisms) | 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. | |
| (2) | Vol. 3, B.9.9, Effects on other non-target organisms (flora and fauna) believed to be at risk | 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. | |

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

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

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (1) | 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) | **Notifier comments**<br>There is no information on the re-entry periods below the heading B.3.5.3. | |

section 2 - Mammalian toxicology (B.6)

**11. Mammalian toxicology (B.6)**

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (1) | Vol. 1, P15, 2.3.2: Proposal for acceptable daily intake (ADI)<br>Vol. 1, P75, 3.1 Background to proposed decision<br>Vol. 3, P79, B.6.3.1: Conclusions<br>Vol. 3, P192, B.6.10.1: Acceptable daily intake | **Notifier's comment**<br>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**'. | |

section 2 - Mammalian toxicology (B.6)

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (2) | Vol. 1, P15, 2.3.2: Proposal for acceptable daily intake (ADI)<br>Vol. 1, P75, 3.1: Background to the proposed decision<br>Vol. 3, P192, B.6.10.1: Acceptable daily intake<br>Vol. 3, P 99, B.6.3.3: 90-day dog with 26 week recovery period, Microscopic pathology<br>Vol. 3, P107, Table B.6.20: Summary of short term toxicity studies with cyflufenamid | **Notifier's comment**<br>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). | |

section 2 - Mammalian toxicology (B.6)

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (3) | Vol. 1, P15, 2.3.2 and P76, 3.1: Proposal for acceptable daily intake (ADI)<br>Vol. 3, P 192, B.6.10.1: Acceptable daily intake<br><br>Vol. 3, P 99, B.6.3.3: 90-day dog with 26 week recovery period<br>Vol. 3, P107, Table B.6.20: Summary of short term toxicity studies with cyflufenamid | **Notifier's comment**<br>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 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. | |
| (4) | Vol. 3, P70, B.6.2.5: Skin irritancy | **Notifier's comment**<br>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. | |
| (5) | Vol. 3, P72, B.6.2.8: Summary of acute toxicity, irritancy and sensitisation | **Notifier's comment**<br>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). | |

section 2 - Mammalian toxicology (B.6)

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (6) | Vol. 3, P76, B.6.3.1<br>Oral studies in rats | **Notifier's comment**<br>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. | |
| (7) | Vol. 3, P76, B.6.3.1<br>Oral studies in rats | **Notifier's comment**<br>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. | |
| (8) | Vol. 3, P79-80, B.6.3.1<br>Oral studies in rats | **Notifier's comment**<br>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. | |

section 2 - Mammalian toxicology (B.6)

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (9) | Vol. 3, P81, B.6.3.1<br>Oral studies in rats | **Notifier's comment**<br>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. | |
| (10) | Vol. 3, P81, B.6.3.1, Table B.6.15 | **Notifier's comment**<br>The following are typographical errors in Table B.6.15:<br>Blood urea nitrogen: insert units of measurement **(mg/dl)**<br>Total bilirubin: amend units to **(mg/dl)** from (µg/dl)<br>Calcium: amend units to **(mg/dl)** from (m/dl)<br>Females terminal body weight at 300 ppm: amend to **294** from 299<br>Testis weight at 300 ppm: Delete **±** | |
| (11) | Vol. 3, P82, B.6.3.1, Table B.6.15 | **Notifier's comment**<br>The following are typographical errors in Table B.6.15:<br>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<br>Female myocardial vacuolation (slight): insert **0** in 0 ppm column and "-" in 50 and 300 ppm columns<br>Female myocardial vacuolation (moderate): insert **0** in 0 ppm column and"-" in 50 and 300 ppm columns | |

* When mentioning page numbers of the DAR in your comments, **the page numbers should refer to the pdf-version** (not the WORD-version) of the DAR to ensure consistency among the Member States.

section 2 - Mammalian toxicology (B.6)

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (12) | Vol. 3, P85, B.6.3.2<br>Oral short term studies in mice | **Notifier's comment**<br>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. | |
| (13) | Vol. 3, P88, B.6.3.2<br>Oral short term studies in mice, Table B.6.16 | **Notifier's comment**<br>The following are typographical errors in Table B.6.16:<br>Terminal body weight of males at 7000 ppm: amend to **36**±2 from 37±2<br>Terminal body weight of females at 1600 ppm: amend to **26**±2 from 27±2 | |
| (14) | Vol. 3, P89, B.6.3.2<br>Oral short term studies in mice | **Notifier's comment**<br>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%)…':<br>i) replace 1000 with **2000** [ppm] and<br>ii) replace 17-38% with **37**-38% . | |
| (15) | Vol. 3, P201, B.6.14.1.1<br>Estimation of operator exposure | **Notifier's comment**<br>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. | |

* When mentioning page numbers of the DAR in your comments, **the page numbers should refer to the pdf-version** (not the WORD-version) of the DAR to ensure consistency among the Member States.

section 2 - Mammalian toxicology (B.6)

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (16) | Vol. 3, P92, B.6.3.3 Oral short term studies in dogs | **Notifier's comment**<br>In Vol. 3, page 92, paragraph 3, line 3, amend 'in males given 500 ppm 30%) to 'in males given 500 ppm **(**30%)' | |
| (17) | Vol. 3, P107, B.6.3.6 Summary of short term toxicity studies, Table B.6.20 | **Notifier's comment**<br>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 | |
| (18) | Vol. 3, P108, B.6.4.1 *In vitro* assays | **Notifier's comment**<br>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**)…'. | |
| (19) | Vol. 3, P109, B.6.4.1 *In vitro* assays | **Notifier's comment**<br>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**)…'. | |
| (20) | Vol. 3, P111, B.6.4.2 *In vivo* studies | **Notifier's comment**<br>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**,….'. | |
| (21) | Vol. 3, P113, B.6.4.3 Summary of genotoxicity studies, Table B.6.21 | **Notifier's comment**<br>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** | |

* When mentioning page numbers of the DAR in your comments, **the page numbers should refer to the pdf-version** (not the WORD-version) of the DAR to ensure consistency among the Member States.

section 2 - Mammalian toxicology (B.6)

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (22) | Vol. 3, P113, B.6.4.3 Summary of genotoxicity studies, Table B.6.21 | **Notifier's comment**<br>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.** | |
| (23) | Vol. 3, P115, B.6.5.1 Oral study in rats (Long-term toxicity and carcinogenicity) | **Notifier's comment**<br>In Vol. 3, page 115, B.6.5.1, Liver, second paragraph, line 4 amend 'Week 13 (21% depression)' to 'Week 13 (**11**% depression)' | |
| (24) | Vol. 3, P125, B.6.5.2 Mouse (carcinogenicity study) | **Notifier's comment**<br>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**…'. | |
| (25) | Vol. 3, P127, B.6.5.2 Mouse (carcinogenicity study), Table B.6.24 | **Notifier's comment**<br>In Vol. 3, page 127, B.6.5.2, Table B.6.24, for <u>males fed 0 ppm</u>:<br>Terminal body weight, amend 57.7 to **57.4**<br>Periportal/centrolobular fat deposition, amend 4 to **11** | |
| (26) | Vol. 3, P127, B.6.5.2 Mouse (carcinogenicity study), Table B.6.24 | **Notifier's comment**<br>In Vol. 3, page 127, Table B.6.24, for <u>females fed 4000/2000 ppm</u>:<br>Fat deposition in cortical tubular epithelium, amend 10 to **10*** <br>Bronchiolar-alveolar carcinoma, amend 3* to **3** | |

* When mentioning page numbers of the DAR in your comments, **the page numbers should refer to the pdf-version** (not the WORD-version) of the DAR to ensure consistency among the Member States.

section 2 - Mammalian toxicology (B.6)

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (27) | Vol. 3, P132, B.6.5.2 b) Supplementary oral carcinogenicity study, Table B.6.26 | **Notifier's comment**<br>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** | |
| (28) | Vol. 3, P135, B.6.5.3 Summary of chronic toxicity and carcinogenicity studies | **Notifier's comment**<br>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. | |
| (29) | Vol. 3, P137, B.6.6.1 Multigeneration study in rats | **Notifier's comment**<br>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. | |
| (30) | Vol. 3, P138, B.6.6.1 Multigeneration study in rats | **Notifier's comment**<br>In Vol. 3, page 138, B.6.6.1, in Conclusions, amend font size of 'in' in line 2.<br>Also, delete '/or' in this line. | |
| (31) | Vol. 3, P138, B.6.6.1 Multigeneration study in rats, Table B.6.28 | **Notifier's comment**<br>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** | |
| (32) | Vol. 3, P140, B.6.6.1 Multigeneration study in rats, Table 6.28 | **Notifier's comment**<br>In Vol. 3, page 140, B.6.6.1, Table B.6.28, delete the last 5 rows as they are duplicated items. | |

section 2 - Mammalian toxicology (B.6)

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (33) | Vol. 3, P147, B.6.6.4 Summary of reproductive toxicity studies, Table 6.31 | **Notifier's comment**<br>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%**' | |
| (34) | Vol. 3, P154, B.6.8.1.2 Enzyme studies, Table B.6.34 | **Notifier's comment**<br>In Vol. 3, page 154, B.6.8.1.2, Table B.6.34, in 'Difference Day 0-14' for 0 ppm:<br>Total BALP3 amend from 3.1± 1.8 to **-3.1± 1.8**<br>LALP amend from 62.2± 15.9 to **-62.2± 15.9** | |
| (35) | Vol. 3, P160, B.6.8.1.3 Hormonal studies | **Notifier's comment**<br>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. | |
| (36) | Vol. 3, P175, B.6.8.1.5 Supplementary studies with the active substance, Table B.6.41 | **Notifier's comment**<br>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**' | |

section 2 - Mammalian toxicology (B.6)

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (37) | Vol. 3, P175, B.6.8.1.5 Supplementary studies with the active substance | **Notifier's comment**<br>In Vol. 3, page 175, B.6.8.1.5, paragraph 1, line 7, delete 'of disturbance'. Negative feedback is a normal mechanism.<br>In line 9, amend 'Thus the thyroid follicular cells seen in…' to 'Thus the thyroid follicular cel**l adenomas** seen in…'. | |
| (38) | Vol. 3, P178, B.6.8.2.1 Acute oral toxicity of the metabolites | **Notifier's comment**<br>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)**'**. | |
| (39) | Vol. 3, P179, B.6.8.2.1 Acute oral toxicity of the metabolites | **Notifier's comment**<br>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'. | |
| (40) | Vol. 3, P190, B.6.10 Summary of mammalian toxicology and proposed ADI, AOEL, ARfD and MAC, Table B.6.43 | **Notifier's comment**<br>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**. | |

section 2 - Mammalian toxicology (B.6)

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (41) | Vol. 3, Appendix 4, Mammalian toxicology references | **Notifier's comment**<br>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. | |

section 3 - Residues (B.7)

**12. Residues (B.7)**

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| | | **Notifier comments**<br>No comments | |

* When mentioning page numbers of the DAR in your comments, **the page numbers should refer to the pdf-version** (not the WORD-version) of the DAR to ensure consistency among the Member States.

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

**13. Environmental fate and behaviour (B.8)**

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| | | **Notifier comments**<br>No comments | |

section 5 - Ecotoxicology (B.9)

**14. Ecotoxicology (B.9)**

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| | | **Notifier comments**<br>No comments | |

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

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (1) | Vol. 1, LOE<br>CIPAC No. | AT: 759 should be added. | |
| (2) | Vol. 1, LOE<br>analytical methods | AT: The LOQs should be added. | |
| (3) | Vol. 3, B.2.1.10<br>UV spectra acidic medium | AT: The value for ε at 361 nm should be inserted at least. | |
| (4) | Vol. 3, B.2.2.14<br>low temperature stability | AT: The precaution on the label should not be supported by missing data but by results of studies.<br>Data concerning low temperature stability are requested. | |
| (5) | Vol. 3, B.5.1.1, B.5.1.3 and B.5.2.1<br>Vol. 4, C.1.4.1<br>analytical methods in general | AT: More information concerning linearity is required (levels, correlation coefficients). | |
| (6) | Vol. 3, B.5.3.2<br>analytical methods water | 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). | |
| (7) | Vol. 3, B.5.3.3<br>analytical methods air | AT: A linearity range of 0.05 – 1.0 µg/mL cannot cover fortification levels of 1 to 100 µg/m$^3$. | |

* When mentioning page numbers of the DAR in your comments, **the page numbers should refer to the pdf-version** (not the WORD-version) of the DAR to ensure consistency among the Member States.

section 2 - Mammalian toxicology (B.6)

**16. Mammalian toxicology (B.6)**

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (1) | Vol. #, <<data point>>, <<description>> | <<MS/notifier>>: <<comment>> | |

* When mentioning page numbers of the DAR in your comments, **the page numbers should refer to the pdf-version** (not the WORD-version) of the DAR to ensure consistency among the Member States.

section 3 - Residues (B.7)

**17. Residues (B.7)**

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (1) | Vol. #, <<data point>>, <<description>> | <<MS/notifier>>: <<comment>> | |

* When mentioning page numbers of the DAR in your comments, **the page numbers should refer to the pdf-version** (not the WORD-version) of the DAR to ensure consistency among the Member States.

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

**18. Environmental fate and behaviour (B.8)**

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (1) | Vol. 3, B.8.6, $PEC_{SW}$, $PEC_{SED}$ | AT: We have FOCUS SW/SED STEP 1 - 4. So, why not use them? | |

* When mentioning page numbers of the DAR in your comments, **the page numbers should refer to the pdf-version** (not the WORD-version) of the DAR to ensure consistency among the Member States.

section 5 - Ecotoxicology (B.9)

**19. Ecotoxicology (B.9)**

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (1) | Vol. 3, B.9.7<br>Other soil non-target macro-organisms | 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. | |

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

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (1) | Vol. 1, General | EFSA: RMS should consider to use the current harmonised version of the list of end points. | |
| (2) | 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. | |
| (3) | Vol. 1, List of end points, active substance, p. 49 | EFSA: It seems that an entry in the box is missing. | |
| (4) | 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. | |
| (5) | 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. | |
| (6) | 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. | |

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

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (7) | 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). | |
| (8) | 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. | |
| (9) | 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 | |
| (10) | 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? | |
| (11) | 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. | |
| (12) | 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. | |

section 2 - Mammalian toxicology (B.6)

**21. Mammalian toxicology (B.6)**

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (1) | 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 package adequately "covers" the potential toxicity of the technical specification. | |
| (2) | Vol 3, B.6.3.3 Oral short term studies in dogs | 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 discussion is needed on the subject.<br>. | |
| (3) | Vol 3, B.6.3.3 Oral short term studies in dogs – Dog oral 12 month study | 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. | |

section 2 - Mammalian toxicology (B.6)

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (4) | Vol. 3, B.6.8.2.3 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). | |
| (5) | Vol 3, B.6.10. 1/2/3 ADI, AOEL, ARfD | 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 considered (e.g. brain vacuolation) and to the different sensitivity of the species investigated. | |

section 3 - Residues (B.7)

**22. Residues (B.7)**

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (1) | Vol. 3, B.7.1.1<br>and Vol. 3, B.7.1.2<br>Wheat metabolism (A) and (B/C) | 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. | The number of days from sowing to harvest or between sampling and final harvest as given in the DAR do not relate to the application of the a.s. and thus is not considered very useful information to evaluate the residue behaviour of the substance. |
| (2) | Vol. 3, B.7.1.1 Wheat metabolism (A), Table B.7.2 | 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. | |
| (3) | Vol. 3, B.7.1.1<br>Vol. 3, B.7.1.2<br>Wheat metabolism (A) and (B/C)<br>and Vol.3, B.7.1.4 Summary/assessment | 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? | |
| (4) | Vol. 3, B.7.1.2 Wheat metabolism (B/C) | EFSA: Is there any idea of what the unknown grain residues (46% TRR) could be? | |

section 3 - Residues (B.7)

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (5) | Vol.3, B.7.2.2 Goat metabolism | EFSA: The major metabolites and main 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. | |
| (6) | Vol.3, B.7.3 Definition of the residue | EFSA: EFSA does not agree with the RMSs' conclusion that residue definition for animal products is not needed.<br>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 acute toxicity than parent and not fully tested.Thus, they might be also considered in a risk assessment residue definition.<br>For risk assessment purposes a residue definition for livestock should be proposed. | With regard to the potential for accumulation of parent see also listing of endpoints toxicology ("equivocal evidence"). A potential for accumulation cannot be excluded and the dosing period in the goat metabolism study was too short to conclude on that issue. |

section 3 - Residues (B.7)

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (7) | Vol.3, B.7.2.2 Goat metabolism | 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. | |
| (8) | Vol.3., B.7.5 Identification of critical GAPs | 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. | |

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

**23. Environmental fate and behaviour (B.8)**

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (1) | Vol. 1, List of end points, Table of intended uses | 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. | |
| (2) | 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. | |
| (3) | 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. | |
| (4) | 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. | |
| (5) | Vol. 3, General | EFSA: A clear statement if studies are considered acceptable by RMS should be included in the DAR. | |

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

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (6) | Vol. 3, B.8.1.1.1 Route of degradation I soil | 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. | |
| (7) | Vol. 3, B.8.1.1.3 Route and rate of degradation in soil – summary and assessment | 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. | |
| (8) | Vol. 3, B.8.2 Soil adsorption and desorption<br><br>Vol. 1, List of endpoints, ads/des box<br>Vol. 1, List of endpoints, PECgw box | EFSA: Please, specify the unit of measure of Koc values. | |
| (9) | Vol. 3, B.8.3 PECsoil | 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. | |
| (10) | Vol. 3, B.8.3 PECsoil | 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. | |

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

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (11) | Vol. 3, B.6.1 PECgw, reference | EFSA: The reference of the original study on PECgw calculations provided by the applicant (and used in the assessment) is not quoted. | |
| (12) | Vol. 3, B.6.1 PECgw, input parameters | EFSA: According to FOCUS, the geometric mean of the DT50field values (25.3 days for the cyflufenamid) should be used in GW modelling. | |
| (13) | Vol. 3, B.6.1 PECgw, modelling | 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. | |
| (14) | Vol. 3, B.8.10 References relied on | EFSA: The reference Brewin (2002) on p.300 is not reported in the list. Please clarify. | |
| (15) | Vol. 3, B.8.10 References relied on | 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. | |

section 5 - Ecotoxicology (B.9)

**24. Ecotoxicology (B.9)**

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (1) | 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). | |
| (2) | Vol. 3, B.9.1.3, Long term toxicity to birds | 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? | |
| (3) | Vol. 3, B.9.1.4, Risk to birds and B.9.3.2, Risk to mammals | EFSA: How was the MAF of 1.1 for the acute risk assessment calculated? | |
| (4) | Vol. 3, B.9.1.4, Risk to birds and B.9.3.2, Risk to mammals | EFSA: Preferably also the risk to birds and mammals from consumption of contaminated drinking water is discussed. | |
| (5) | 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. | |
| (6) | Vol. 3, B.9.2.3.2, Long term toxicity to *D. magna* | 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. | |

* When mentioning page numbers of the DAR in your comments, **the page numbers should refer to the pdf-version** (not the WORD-version) of the DAR to ensure consistency among the Member States.

section 5 - Ecotoxicology (B.9)

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (7) | Vol. 3, 9.2.4.4, Risk to aquatic organisms | 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). | |
| (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.<br>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. | |
| (9) | Vol. 3, B.9.3.1, Toxicity to mammals | EFSA: The NOEC for mammals was set at 75 mg/kg bw based on the study by Patten (2000a, b and c).<br>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. | |

section 5 - Ecotoxicology (B.9)

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (10) | 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 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. | |
| (11) | Vol. 3, B.9.6.2.3, Long term toxicity to earthworms | 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. | |
| (12) | 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. | |
| (13) | Vol. 3, B.9.8.1.3, Effects on soil micro-organisms | EFSA: Given the $DT_{90field}$ for cyflufenamid, a study on soil micro-organisms with the lead formulation should be envisaged. | |

* When mentioning page numbers of the DAR in your comments, **the page numbers should refer to the pdf-version** (not the WORD-version) of the DAR to ensure consistency among the Member States.

section 5 - Ecotoxicology (B.9)

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (14) | Vol. 3, B.9.8.1.3, Effects on soil micro-organisms | 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. | |
| (15) | Vol. 3, B.9.9.2, Risk to non-target fauna and flora | 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). | |
| (16) | 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. | |
| (17) | 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. | |