PEER REVIEW REPORT ON **LENACIL** 28 09 2009

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Comments on the Draft Assessment Report on lenacil (EAS)

RMS BE

End of commenting period: 20.02.2008 (NOT) and 10.03.2008 (MS)

| Date | Supplier | File |
|---|---|---|
| 14.02.2008 | Notifier | 01 lenacil comments NOT 2008-02-14.doc |
| 06.03.2008 | Germany | 02 lenacil comments DE 2008-03-06.doc |
| 07.03.2008 | France | 03 lenacil comments FR 2008-03-07.doc |
| 10.03.2008 | United Kingdom | 04 lenacil comments UK 2008-03-10.doc |
| 10.03.2008 | The Netherlands | 05 lenacil comments NL 2008-03-10.doc |
| 11.03.2008 | Austria | 06 lenacil comments AT 2008-03-11.doc |
| 13.01.2009 | EFSA | 07 lenacil comments EFSA 2009-01-13.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. 3, B.4.1 (page 56)<br>Vol 1, 2.1.4 (page 16)<br>Proposed classification of the active substance | Notifier: The notifier does not agree with a classification of R64. (see Mammalian toxicology (B.6) comment 5) | |
| (2) | Vol 1, 4.5 (page 93) | Notifier: Since a fully validated method for the determination of lenacil residues in sugar beet is available for monitoring purposes, the notifier considers that there is no need for additional information to be submitted. | |
| (3) | Vol 1, 4.2 (page 93)<br>Suspensibility and wettability | Notifier: Venzar 80 WP has been sold for over 30 years and has performed satisfactorily in the field in many countries including Belgium, France and the UK. The notifier has received no complaints over the sprayability of the product and no complaints of poor efficacy linked to sprayability. Venzar 80 WP product labels already include a statement warning users that agitation should be started before loading and maintained during spraying. | The notifier agrees with the RMS that this issue can be addressed at member state level during the re-registration of Venzar 80 WP. Evidence of satisfactory importance and homogeneity of the diluted spray solution in the form of efficacy data will be submitted in the biological assessment dossier to member state authorities. |

## 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. 3 B6.3.2.1 page 17, Oral 90-d toxicity<br><br>Vol. 3 B6.10, Page 63. Short term toxicity<br><br>Vol. 1, page 18-21 point 2.3, Impact on human and animal health | Notifier: Additional information pertinent to discussions about possible target organs and possible effects on thyroid function affecting determination of adverse effect levels was submitted by the Notifier in the dossier. The Notifier requests inclusion of this information at relevant points in the summary of repeated dose toxicity evaluations.<br><br>Alterations to text and endpoints are requested on basis of arguments relating to thyroid function tests and adaptive liver responses. | Additional histopathological examinations were completed for this study and are presented in the updated summary dossier Annex point IIA 5.3.2.1.1.<br><br>Following observation of thyroid changes in the multi-generation reproductive toxicity study additional histopathological examinations of thyroid tissue preserved from a 13 week dietary study in rats were instigated. In the original study (Point IIA 5.3.2.1) thyroids from the control and high dose (50000 ppm) groups were examined. The additional investigation extended the examination to the low and intermediate groups. The study authors concluded that examination of sections stained with haematoxylin and eosin revealed no changes indicative of any accumulation of pigment in the follicular epithelium, or any other change indicative of a response to treatment. Schmorl's staining of the thyroids, however, revealed a background level of Schmorl's positive staining in all groups, particularly in males. Schmorl's positive staining is indicative of lipofuscin in the follicular epithelium. There was a treatment-related increase in the incidence and severity of Schmorl's-positive staining in females given lenacil technical at 50000 ppm, and a slight increase in the severity of this finding in males given 50000 ppm. The slightly increased incidence of Schmorl's-positive staining in females given 5000 ppm was within the background incidence and was, therefore, not attributed to treatment. Following a recovery period of four weeks there were no significant differences in incidence of Schmorl's-positive staining between control and high dose group males or females.<br><br>Further thyroid function tests were also completed in female rats dosed for 20 weeks at 250 or 50000 ppm lenacil. Investigations included assessment |

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| | | | of T3 and T4 levels, thyroid weights, $^{125}$Iodide uptake and displacement. The study concluded that there was no evidence to suggest that lenacil technical at doses of up to 50000 ppm affected the ability of the thyroid to take-up and organify $^{125}$Iodide. Measurements of T3 during the study also indicated that lenacil does not act as an inhibitor of the deiodinase which converts T4 to T3. Overall, the results of the study showed that lenacil technical was not directly toxic to the thyroid.<br><br>The conclusion to this summary states 500 ppm to be a NOEL. It appears that the RMS has also concluded 500 ppm to be the NOAEL. From the results presented it is apparent that changes in the two higher dose levels were inconsistent and generally showed no clear dose relationship. While an effect of treatment is clearly apparent at 5000 ppm, this is not the case at the intermediate dose level where reduced monocytes and a slight increase in urinary protein were the only changes of note, both showing recovery after removal of treatment, indicating no adverse long term effects of lenacil administration. There was no corroborative evidence from macroscopic or microscopic findings to confirm any adverse effects of treatment at 5000 ppm.<br><br>The lowest NOEL derived from short-term toxicity studies in rat, mouse and dog was based on the results of the 90-day rat study and set at 40.6 mg/kg/day (500 ppm). The lowest appropriate NOAEL value was derived from the same study as the intermediate dose level of 412 mg/kg/day (5000 ppm). This was based on adaptive liver changes at the highest dose of 50000 ppm, which constituted the LOAEL. The NOAEL was defined by reduced white blood cell numbers at 5000 ppm, considered of uncertain toxicological significance, in that the findings were not consistently seen in the long-term rat study. There were no bodyweight effects at any dosage. |

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|---|---|---|---|
| | | | In the opinion of the notifier, the data support the conclusion indicating an NOAEL in the rat 90 day study of 5000 ppm and a NOEL of 500 ppm. |
| (2) | Vol. 3 B6.3.2.2 page 21, Oral 90-d toxicity - dog | Notifier: Discussions relating to the adaptive nature of the hepatic response have been partially included in the DAR as a comment from Notifier. The Notifier requests expansion of this comment to include more details pertinent to the "adaptive response argument". | The notifier proposes including the following additional text in the DAR:<br><br>With the exception of increased liver weight, the minor changes noted in various haematological, blood chemistry, urinalysis, organ weight and pathology parameters show no dose relationship, no trends for increasing effect over time or with increasing dose and show no consistency between the sexes. The response in the liver is clearly an adaptive response to increase metabolic workload. The effects on liver weight, alkaline phosphatase and hepatic histopathology are consistent with an adaptive response which does not indicate an adverse effect of treatment.<br><br>The findings in the 28 day dog study and 90 day dog study do not show good correlation indicating the minor disturbances are not real toxic changes. The RMS expressed concern about renal dysfunction following the 28 day study but the 90 day study provides no evidence to support the proposition of renal effects. Opposing effects occurred in haematology parameters in the two studies. |
| (3) | Vol. 3 B6.3.4, Page 22 Summary of short term toxicity<br><br>Vol. 3 B6.10, Page 63. short term toxicity | Notifier: A revised table of results is proposed with different endpoints taking into account the adaptive liver response and additional thyroid function tests. | Additional histopathological examinations were completed for this study and presented in the updated summary dossier at Annex point IIA 5.3.2.1.1. See text in Column 3 for Comment (1) above.<br><br>For the 90 day rat study, additional investigations relating to thyroid function demonstrate the non-adverse nature of the findings at the LOAEL defined in table above (5000 ppm).<br><br>It is the opinion of the notifier that, based on the overall response to 13 weeks administration and evidence of recovery, the appropriate NOAEL derived from short term toxicity studies is 412 mg/kg/day (5000 ppm). |

<table>
<tr><th>No.</th><th>Column 1<br>Reference to draft assessment report *</th><th>Column 2<br>Comment * (restricted to 500 characters, ca.10 lines)</th><th>Column 3<br>Further explanations</th></tr>
<tr><td></td><td></td><td></td><td>This conclusion was based on the occurrence of adaptive liver changes at the highest dose of 50000 ppm, which constituted the LOAEL. The NOAEL was defined by reduced white blood cell numbers at 5000 ppm, considered of uncertain toxicological significance, in that the findings were not consistently seen in the long-term rat study.<br><br>A revised Table B.6.3.4-1 for the DAR is presented below:
<table>
<tr><th rowspan="2">Type of test<br>Test species</th><th rowspan="2">Test substance<br>purity</th><th colspan="4">Results</th><th rowspan="2">Reference</th></tr>
<tr><th>NOEL</th><th>NOAEL (mg/kg bw/day)</th><th>LOAEL (mg/kg bw/day)</th><th>Symptoms at LOAEL</th></tr>
<tr><td>90 day dietary study , rat+ 4 week recovery Period</td><td>Batch n° 141712003 ; purity 98.6%</td><td>500ppm (40.6mg/kg bw/d)</td><td>5000ppm (412mg/kg bw/d)</td><td>50000ppm (5029mg/kg bw/d)</td><td>leucopenia, ↑excretion urinary proteins; lipofuscin staining in thyroid follicular epithelium</td><td>Thirlwell, 2002b,c</td></tr>
<tr><td>90 day dietary study, mice</td><td>Batch n° 9038; purity 98.2%</td><td>100 ppm (15.5 mg/kg bw/d)</td><td>1000 ppm (157 mg/kg bw/d)</td><td>5000 ppm (787 mg/kg bw/d)</td><td>leucopenia in male and female mice</td><td>Malley,1991</td></tr>
<tr><td>90 day dietary study, dog</td><td>Batch n° 141712003 ; purity: 98.6%</td><td>1000 ppm (44 mg/kg bw/d)</td><td>25000 ppm (1121 mg/kg bw/d)</td><td>>25000 ppm (1121 mg/kg bw/d)</td><td>Adaptive liver changes: ↑ relative liver weight in female dogs, centrilobular/midzonal hepatocyte hypertrophy</td><td>Geary,2002</td></tr>
</table></td></tr>
<tr><td>(4)</td><td>Vol. 3 B6.5.2, page 37 Carcinogenicity in the rat</td><td>Notifier: Request for inclusion of additional comment relating to the derivation of the NOEL</td><td>The notifier agrees with the study author conclusions in relation to endpoints determined for long term studies – based on rat and mouse</td></tr>
</table>

| 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 |
|---|---|---|---|
| | | and NOAEL values in this study – see text in column 3. | oncogenicity investigations. The NOEL and NOAEL values proposed were unchanged by the thyroid function assessments. The value proposed for the rat NOEL is 250 ppm (12.0 and 15.9 mg/kg/day in males and females respectively) and for the rat NOAEL is 2500 ppm (118 and 160 mg/kg/day in males and females), based on slightly reduced motor activity in males, and the LOAEL was the highest dose tested, 25000 ppm, where, in our opinion, adaptive liver changes were seen in males and non-specific toxicity in females. There were no neoplastic lesions apparent in the rat and the non-neoplastic liver lesions were indicative of an adaptive response. The neoplastic lesions seen in the mouse were species-specific and not relevant to human risk assessment.<br><br>The RMS has concluded from the available data and background information that malignant adenocarcinoma incidence is well within the background incidence for the animal supplier and "in the absence of dosage relationship, the increase in adenocarcinoma is not considered to be associated with the administration of Lenacil" and therefore the responses at 2500ppm and 25000 ppm were deemed equivocal. However, the endpoint subsequently used to set an NOAEL for oncogenicity is below the level of these equivocal findings.<br><br>The Notifier suggests that the data support the proposition that the administration of lenacil is not associated with mammary tumour incidence, since the incidence at high dose levels is less than that in background data. The Notifier proposes that the same information is used to set a NOAEL for oncogenicity, where, if lenacil is not associated with induction of any of the tumours observed, as concluded by Notifier and supported by RMS in text above, then 2500 ppm is the appropriate NOAEL. |

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| (5) | Vol. 3 B6.6.1, page 44 Two generation reproduction toxicity in the rat<br><br>Vol. 3 B6.6.3, Page 53-54. Summary of reproductive toxicity and teratogenicity | Notifier: The Notifier disagrees with the conclusion of the RMS to classify the active substance with R64. In the DAR the RMS proposes further discussion in relation to this classification. The notifier requests inclusion of arguments from the dossier summaries in the DAR which conclude that R64 is not required (see Column 3) and amendment of the conclusions. | The relevant legislation is Council Directive 67/548/EEC, as amended by Commission Directive 2001/59/EC, Annex 6 (Annex VI) Section3 2.8 and 4.2.3.3.<br><br>Section 3.2.8 states the criteria for R64 as: For substances and preparations which are absorbed by women and may interfere with lactation or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child.<br><br>In rat metabolism studies, lenacil is primarily excreted via urine as water-soluble hydroxyl metabolites. It is generally considered that the high fat content of milk may lead to fat-soluble substances and metabolites being present in the milk. Residues in the target crop, sugar beet, are also hydroxyls and ketones, and it is predicted that in humans, these will be further hydroxylated and excreted via urine. There is no evidence that lenacil or its metabolites accumulate in the body, such that there is no implication that mobilisation of maternal fat reserves could lead to the presence of lenacil or its metabolites in milk. The ADI for Lenacil is 0,014 mg/kg bw/day. The NOAEL proposed by the RMS is 10,000 ppm or 1,727 mg/kg bw/day. This gives a margin of safety in excess of 120,000. The criterion for R64 includes the words „in amounts sufficient to cause concern'.<br><br>Furthermore, Section 4.1.3.3 states that „For the purpose of classification, toxic effects on offspring resulting only from exposure via the breast milk, or toxic effects resulting from direct exposure of children will not be regarded as Toxic to reproduction, unless such effects result in impaired development of the offspring'.<br><br>It is accepted that offspring bodyweights were slightly lower than controls |

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| | | | in the F0F1 (by 6%) and F1F2 (by 11%) during the lactation period, but offspring survival was not adversely affected, and the bodyweights of the F0F1 pups selected for the F1 generation were not different from controls at the start of the pre-mating maturation period. Also, the behavioural and developmental landmarks assessed prior to and after weaning were not adversely affected by either maternal treatment or by direct intake of the test material. Any marginal bodyweight effects on offspring prior to weaning are considered transient, and insufficient evidence for adverse effects via maternal milk.<br><br>The legislation states: „This R-phrase may also be appropriate for substances which affect the quantity or quality of the milk'. Where there is an effect on quantity of the milk, there is usually evidence from the immediate post-partum period. The body wall of the newborn rat is translucent, and the technicians can see the presence of milk in the pups' stomach as a whitish crescent in the abdomen. Absence of this crescent is recorded in the data for the study as an indication that the dam is not nursing the pups. It is frequently accompanied by high post natal mortality in pups. Neither finding was made in this study.<br><br>The legislation gives further guidance:<br>R64 would normally be assigned on the basis of:<br>(a) toxicokinetic studies that would indicate the likelihood that the substance would be present in potentially toxic levels in breast milk; and/or<br>(b) on the basis of results of one or two generation studies in animals which indicate the presence of adverse<br>effects on the offspring due to transfer in the milk; and/or<br>(c) on the basis of evidence in humans indicating a risk to babies during the lactational period. |

<table>
<tr><th>No.</th><th>Column 1<br>Reference to draft assessment report *</th><th>Column 2<br>Comment * (restricted to 500 characters, ca.10 lines)</th><th>Column 3<br>Further explanations</th></tr>
<tr><td></td><td></td><td></td><td>The evidence from metabolism studies is that lenacil or its' metabolites would not be preferentially excreted in the milk, and if present at all, would be at a minute fraction of levels considered NOAEL in the rat. The effects on the offspring are minor, transient and there is no indication of impaired development or reduced survival. Finally, there is no evidence in humans.<br><br>In conclusion, the Notifier believes lenacil should not be classified R64.</td></tr>
<tr><td>(6)</td><td>Vol. 3 B6.6.1, page 44<br>Two generation reproduction toxicity in the rat</td><td>Notifier: The notifier requests inclusion of the discussion of thyroid function tests in relation to interpretation of multigeneration study endpoints in the DAR.</td><td>See text in Column 3 for Comment (1) above.</td></tr>
<tr><td>(7)</td><td>Vol. 3 B6.10.1, Page 68. ADI<br><br>Vol. 1, page 23 point 2.3.2, ADI</td><td>Notifier: The Notifier proposes an ADI of 1.18 mg/kg/day.<br><br>The notifier requests inclusion of a table summary of revised endpoints on which to base derivation of the ADI in the DAR taking account of thyroid function and adaptive liver responses in long term toxicity studies..</td><td>The revised table of endpoints for derivation of the ADI is presented below:<br>The NOAEL values are those considered appropriate by the Notifier based on an assessment of the occurrence of toxicologically significant adverse effects.<br><br>-Summary of relevant NOAELs for deriving the ADI
<table>
<tr><th rowspan="2">Study</th><th colspan="2">NOAEL</th></tr>
<tr><th>ppm diet</th><th>mg/kg/day equivalent</th></tr>
<tr><td>Rat chronic toxicity</td><td>2500</td><td>Males: 139.1<br>Females: 188.5</td></tr>
<tr><td>Rat oncogenicity</td><td>2500</td><td>Males: 118<br>Females: 160</td></tr>
<tr><td>Mouse oncogenicity</td><td>2500 (males)<br>7000 (females)</td><td>Males: 332<br>Females: 1358</td></tr>
<tr><td>Rat multigeneration</td><td>10000 (non-reproductive NOAEL)</td><td>Dams and progeny 817</td></tr>
</table>
It is the opinion of the notifier that these endpoints adequately take account of minor changes observed in various studies and gives suitable</td></tr>
</table>

| 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 |
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| | | | weight to the consideration of adverse and non-adverse toxicological findings. The thyroid effects, adaptive liver changes, tumour incidence below animal supplier's background or sporadic incidence levels and absence of real effects on newborn pups have been discussed in earlier comments.<br><br>From this table it is apparent that the lowest NOAEL is 118 mg/kg/day based on the rat oncogenicity study. It is appropriate to apply an uncertainty factor of 100 to the NOAEL of 118 mg/kg/day and the Notifier proposes an ADI of 1.18 mg/kg/day. |
| (8) | Vol. 3 B6.10.3, Page 69.<br><br>Vol. 1, page 17 point 2.3.4, AOEL | Notifier: The Notifier proposes an AOEL of 4.12 mg/kg/day. The notifier proposes inclusion of a table summary of revised endpoints on which to base derivation of the AOEL in the DAR taking account of thyroid function and adaptive liver responses in short and long term toxicity studies. | The revised table of endpoints for derivation of the AOEL is presented below:<br>The most sensitive species, from rat, mouse and dog, tested in short term studies was the rat. It is proposed to set an AOEL based on the No Adverse Effect Level in a 90 day dietary study in the rat of 5000 ppm. The relevant NOAEL values from short term toxicity and developmental toxicity studies appropriate for derivation of the AOEL are as follows: |

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|---|---|---|---|

**-Summary of relevant lowest NOELs/NOAELs for derivation of the AOEL**

| Study type | NOEL | | NOAEL | | References |
|---|---|---|---|---|---|
| | ppm diet | mg/kg/day | ppm diet | mg/kg/day | |
| 13-wk feeding rat | 500 | 40.6 | 5000 | 412 | 5.3.2.1 |
| 13-wk feeding mouse | 1000 | 157 | 10000 | male 1616<br>female 2150 | 5.3.2.2 |
| 13-wk feeding dog | 1000 | 44 | 25000 | male 1121<br>female 1102 | 5.3.2.3 |
| Developmental toxicity rat (gavage) | - | 1000 | -- | 1000 | 5.6.2.1 |
| Developmental toxicity rabbit (gavage) | - | 1000 | -- | 1000 | 5.6.2.2 |

The lowest NOEL derived from short-term toxicity studies in rat, mouse and dog was based on the results of the 90-day rat study and set at 40.6 mg/kg/day (500 ppm). The lowest appropriate NOAEL value was derived from the same study as the intermediate dose level of 412 mg/kg/day (5000 ppm). This was based on adaptive liver changes at the highest dose of 50000 ppm, which constituted the LOAEL. The NOAEL was defined by reduced white blood cell numbers at 5000 ppm, considered of uncertain toxicological significance, in that the findings were not consistently seen in the long-term rat study. There were no bodyweight effects at any dosage.

The systemic AOEL ($AOEL_{SYS}$) is derived from the 5000 ppm No Observed Adverse Effect Level (NOAEL) in the rat 90-day repeat dose oral toxicity study which corresponded to an achieved mean daily intake of 412 mg/kg/day. A standard 100-fold safety factor has been used to allow for inter- and intra- species variations without adjustment for either toxicokinetic or toxicodynamic components. This default safety factor provides a high degree of conservatism in the calculation of the AOEL.

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| | | | Following review of absorption data, no correction for calculation of the systemic (internal) dose was considered appropriate since the estimated oral absorption (circa 74%) did not represent a significant difference between applied and absorbed dose and oral absorption reached 85% of the dose within 48 h. Consequently, the Notifier proposes $AOEL_{SYS}$:<br>$412 \div 100 \quad x\ 1^{a} = 4.12$ mg/kg/day<br><br>a: No correction factor included for oral absorption of at least 74% (estimated by notifier in summary dossier presented in June 2006), estimated from combined urinary and biliary excretion, following single or repeated oral administration to rats or 85% when measured over 48 h (higher mean absorption value of 85% derived by RMS for 48 hour period, the notifier accepts the argument for use of the higher value for absorption). The use of default safety factors for inter and intra species variation (10 fold in each case) provide a highly conservative estimate of the AOEL, not requiring further refinement for systemic availability. |
| (9) | Vol. 3 B6.11.3, Page 71 Acute inhalation toxicity to rats of Venzar 80 WP. | Notifier: A complete copy of the report is available and has been submitted to include pages originally omitted in error. | The deviations from official protocol cited appear to be based on the EPA protocol rather than EC/OECD criteria. |
| (10) | Vol. 3 B6.12, Page 74 Dermal absorption. | Notifier: Comments relating to derivation of the correct dermal absorption values for diluted and undiluted forms of lenacil are included in the DAR but the references cited to support the Notifier's argument have been omitted. We request inclusion of the references. See column 3 for full reference. | Refs 1 and 2:<br>Opinion of the Scientific Committee on Plants on Commission Draft Guidance on Dermal Absorption (Doc. SANCO/222/2000 rev 4). SCP/Guide-DERM/002 Final 30 April 2002.<br><br>Opinion of the Scientific Committee of Cosmetic Products and Non Food \|Products intended for Consumers. Basic Criteria for the *In Vitro* Assessment of Dermal Absorption of Cosmetic Ingredients. . SCCNFP/075/03 – October 2003. |
| (11) | Vol. 3, B.6.15.1 (page 76) Estimation of operator exposure: data used for the calculation | Notifier: Operator body weight should read 60 kg (UK model) **and 70 kg (German model)** | |

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<table>
<tr><th>No.</th><th>Column 1<br>Reference to draft assessment report *</th><th>Column 2<br>Comment * (restricted to 500 characters, ca.10 lines)</th><th>Column 3<br>Further explanations</th></tr>
<tr><td>(12)</td><td>Vol. 3, B.6.15.1 (page 76) Estimation of operator exposure: Table B.6.15.1-1</td><td>Notifier: The exposure estimated using UK POEM is reduced for operators using RPE during mixing/loading (as permitted in the UK model) in addition to gloves during mixing and loading and application.</td><td>Amended Table B.6.15.1-1 is shown below:<br>Table B.6.15.1-1: Estimated operator exposure (mg/person/day) according to the UK POEM
<table>
<tr><th rowspan="2">Product/ Application method/ crop</th><th colspan="3">Dermal absorbed dose (mg/day)</th><th colspan="3">Inhalation exposure (mg/ day)</th><th rowspan="2">Total exposure (mg /day)</th></tr>
<tr><th>Mix/load</th><th>Spray</th><th>Total</th><th>Mix/load</th><th>Spray</th><th>Total</th></tr>
<tr><td>Tractor mounted/trailed boom sprayer ; hydraulic nozzles</td><td>9.18</td><td>35.52</td><td>44.7</td><td>16.475</td><td>0.15</td><td>16.62</td><td>61.32</td></tr>
<tr><td>Type of protection</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Gloves M/L + A RPE (FFP2) M/L</td><td>0.0918</td><td>5.514</td><td>5.605</td><td>1.647</td><td>0.15</td><td>1.797</td><td>7.404</td></tr>
</table></td></tr>
</table>

* 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.

<table>
<tr><th>No.</th><th>Column 1<br>Reference to draft assessment report *</th><th>Column 2<br>Comment * (restricted to 500 characters, ca.10 lines)</th><th>Column 3<br>Further explanations</th></tr>
<tr><td>(13)</td><td>Vol. 3, B.6.15.1 (page 77) Estimation of operator exposure: Table B.6.15.1-3 and Conclusions<br><br>Vol. 1, 2.3.6 Operator exposure (page 24).<br><br>Vol. 1 List of endpoints (page 45)</td><td>Notifier: The exposure estimated using UK POEM is less than the AOEL (77%) for operators wearing RPE (FFP2 particle filtering mask) during mixing and loading in addition to gloves during mixing and loading and application.</td><td>Amended Table B.6.15.1-3 is shown below:<br><br>Table B.6.15.1-3: Exposure as a proportion of AOEL- POEM model.<br><table><tr><th rowspan="2">Product/<br>Application method/<br>crop</th><th colspan="2">Total systemic exposure – 60 kg person (mg/kg bw/day)</th><th colspan="2">% of AOEL</th></tr><tr><th>no PPE worn</th><th>PPE worn*</th><th>no PPE worn</th><th>PPE worn</th></tr><tr><td colspan="5">Tractor mounted/trailed boom sprayer ; hydraulic nozzles</td></tr><tr><td></td><td>1.022</td><td>0.123</td><td>638</td><td>77</td></tr></table>* : Gloves M/L + A plus RPE (FFP2 particle filtering mask) during mixing/loading.<br><br>Under Conclusions in B.6.15.1, the following statement is proposed: The use of gloves during M/L and A and RPE (FFP2, particle filtering mask) during M/L brings a reduction of exposure to below the AOEL.<br><br>In Vol 1 2.3.6, the following is proposed under Operator Exposure: The results demonstrate that exposure of operators during the application of lenacil under field conditions is lower than the AOEL according to the German model without PPE, and lower than the AOEL according to the UK model with gloves during mixing/loading and application, and RPE during mixing/loading.<br><br>In Vol. 1 list of endpoints, the following is proposed under Exposure Scenarios, Operator:<br>UK model, tractor mounted equipment without PPE: 638% of AOEL, with PPE (gloves and RPE): 77% of AOEL.</td></tr>
</table>

section 2 - Mammalian toxicology (B.6)

<table>
<tr><th>No.</th><th>Column 1<br>Reference to draft assessment report *</th><th>Column 2<br>Comment * (restricted to 500 characters, ca.10 lines)</th><th>Column 3<br>Further explanations</th></tr>
<tr><td>(14)</td><td>Vol. 3, B.6.15.1 (page 76)<br>Estimation of operator exposure: Table B.6.15.1-2</td><td>Notifier: The values in Table B.6.15.1-2 are not presented in the same way as those in Table B.6.15.1-1. Currently, the tables imply that estimated exposure using the German model is higher than with the UK POEM. The notifier suggests that the values in Table B.6.15.1-2 are corrected for dermal absorption values (the values proposed by the RMS) to be consistent with Table B.6.15.1-1.</td><td>Amended Table B.6.15.1-2 is shown below:<br><br>Table B.6.15.1-2: Estimated operator exposure (mg/person/day) according to the GERMAN Model<br><table><tr><th rowspan="2">Product/ Application method/ crop</th><th colspan="3">Dermal exposure (mg/day)</th><th colspan="3">Inhalation exposure (mg/ day)</th><th rowspan="2">Total exposure (mg /day)</th></tr><tr><th>Mix/load</th><th>Spray</th><th>Total</th><th>Mix/load</th><th>Spray</th><th>Total</th></tr><tr><td>Tractor field crop</td><td>1.62</td><td>6.98</td><td>8.60</td><td>0.7</td><td>0.01</td><td>0.71</td><td>9.31</td></tr><tr><td>Type of protection</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Gloves M/L + A</td><td>0.0162</td><td>5.690</td><td>5.71</td><td>0.7</td><td>0.01</td><td>0.71</td><td>6.42</td></tr></table></td></tr>
<tr><td>(15)</td><td>Vol. 3, B.6 Appendix: (page 85)<br>Estimation of the exposure (page 88-89)</td><td>Notifier: There are errors in the spreadsheets for exposure calculated by UK POEM. In addition, amended calculations showing how exposure is reduced by RPE (FFP2 particle filtering mask) during mixing and loading.</td><td>Corrected/amended operator exposure spreadsheet calculations are shown below.<br><br>For confidentiality reasons the table has been removed by EFSA</td></tr>
</table>

* 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)

### 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 |
|---|---|---|---|
| | | Notifier: No comments. | |

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

**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.8.1.1.1, Aerobic Degradation in Soil | Notifier: Typographical error, page 8-2, final paragraph, second sentence. „Radioactivity of the Soxhlet extracted soil' should be replaced by „Radioactivity in the Soxhlet extracted soil' | |
| (2) | Vol. 3, B.8.1.2.1, Aerobic Degradation | Notifier: Typographical error, page 8-8, first paragraph, final sentence. „Up t0' should be replaced by „Up to'. | |
| (3) | Vol. 3, B.8.1.2.1, Aerobic Degradation | Notifier: Typographical error. Page 8-13, second paragraph. „The major degradation product Metabolite IN-KF313 reached maximum level of 14.7% AR after 14 days; Metabolite IN-KE121 reached maximum level of 13.9 % AR after 14 days' should be replaced by „The major degradation product Metabolite IN-KF313 reached a maximum level of 14.7% AR after 14 days; Metabolite IN-KE121 reached a maximum level of 13.9 % AR after 14 days'. | |
| (4) | Vol. 3, B.8.1.2.1, Aerobic Degradation | Notifier: Typographical error, page 8-17, third paragraph, final sentence. Duplication of to. | |
| (5) | Vol. 3, B.8.1.2.1, Aerobic Degradation | Notifier: Table 8.1.2.1-16. Observed DT50 values for Sheringham and Wick soils should be given as 12 and 10 days, respectively. The data will then be consistent with the report by Shaw (2004) and allow the derivation of DT50 (reference conditions) for these soils as shown in the table. | |

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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.8.1.2.1, Aerobic Degradation | Notifier: Proposed geometric mean for IN-KE121 based in the data given in Table 8.1.2.1-16 should be 5.0 days and not 5.1 days as written. | |
| (7) | Vol. 3, B.8.1.3.1, Soil Dissipation Testing | Notifier: Typographical error, page 8-21, fourth paragraph, final sentence. Delete final parenthesis. | |
| (8) | Vol. 3, B.8.2.4, Lysimeter and Field Leaching Studies | Notifier: Typographical error, page 8-28, first paragraph, second sentence. Duplication of for. | |
| (9) | Vol. 3, B.8.4.4, Water Sediment Study | Notifier: Typographical error, page 8-37, experimental design, first paragraph, first sentence. With and height are spelled incorrectly. | |
| (10) | Vol. 3, B.8.4.5, Degradation in the Saturated Zone | Notifier: Typographical error, page 8-43, first sentence. The word no should be deleted. | |
| (11) | Vol. 1, 2.5.1, Definition of the Residue Relevant to the Environment | Notifier: Justification for non-inclusion of IN-KE121 in the definition of the residue is presented in Vol 3, B.8.10. For completeness the justification in Vol 3 should be reproduced under Vol 1, 2.5.1. | |
| (12) | Vol. 1, 2.5.3, Fate and Behaviour in Water | Notifier: Page 32, second paragraph, fourth sentence. To give the correct meaning to the sentence, the word „this' should be replaced by IN-KF313. | |
| (13) | Vol 1. List of End Points, Rate of Degradation in Soil | Notifier: The geometric mean soil degradation rate for lenacil should be given as 10.25 days to be consistent with the value shown in Vol 3. B.8.1.2.1, page 8-17. | |

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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 |
|---|---|---|---|
| (14) | Vol 1. List of End Points, Rate of Degradation in Soil | Notifier: The geometric mean soil degradation rate for IN-KF313 should be given as 11.5 days to be consistent with the value shown in Vol 3. B.8.1.2.1, page 8-18. The table identifier for IN-KF313 should state geometric mean rather than arithmetic mean. | |
| (15) | Vol 1. List of End Points, Rate of Degradation in Soil | Notifier: The geometric mean soil degradation rate for IN-KE121 should be given as 5.0 days and the DT50 value for IN-KE121 at 20°C pF2/10kPa should be corrected from 3.0 to 7.3 days. | |
| (16) | Vol 1. List of End Points, Rate of Degradation in Soil | Notifier: The field $DT_{50}$ and $DT_{90}$ values for lenacil are not consistent with those given in Vol 3. Table 8.1.3.1-2. The $DT_{50}$ values should be 25, 28, 18 and 88 days for the French, German, German and Spanish soils, respectively. The corresponding $DT_{90}$ values should be 84, 91, 61 and 291 days, respectively. | |
| (17) | Vol 1. List of End Points, Rate of Degradation in Soil | Notifier: The maximum formation of IN-KF313 in the Ruckhaltebecken sediment is incorrectly given as 2.7% after 120 days. The correct value should be 3.0% after 88 days. | |

section 5 - Ecotoxicology (B.9)

**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 |
|---|---|---|---|
| | | Notifier: No comments. | |

**6. 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, B.5.2.1 | DE: Conclusion of Tilkes, 1998: Because only 1 recovery experiment per level was reported, we consider this study as being not acceptable. If RMS agrees, please state clearly. | |
| (2) | Vol. 3, B.5.2.2 | DE: Method of Wittig, 2002: We agree that one UV spectrum of a standard is shown in this study. But this was a spectrum of a pure standard without any information on its concentration level. Therefore, we do not agree with the RMS that confirmation of the primary method was acceptable.<br>Therefore a data gap exists and a confirmatory method for the determination of the active substance in drinking water and surface water is missing. | According to SANCO confirmation by UV-spectra requires "an UV-spectrum under the conditions of the determination". From our point of view this requires the comparison of UV-spetra of standard and fortified real sample generated by LC-DAD at the LOQ. This is not done in the study. |
| (3) | Vol. 3, B.5.5.3,<br>Vol. 1, 2.2.3 (p. 16),<br>List of End points (p. 43), 4.5 (p. 93) | DE: We consider analytical methods for water (drinking water, surface water) as being not fully validated. A confirmatory method for drinking water and for surface water is missing. (please refer to comment No. 2). Please correct the respective text sections and tables. | |

**7. 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, 2.1.4, Classification and labelling | DE: A possible need for classification and labelling for carcinogenicity (R40) on the basis of thyroid and mammary tumours in female rats should be discussed on the PRAPeR meeting. Lung tumours in male mice must also be taken into account. If a carcinogenic effect is recognized and a NOAEL for oncogenicity is set for a particular substance (as this was the case in the DAR), allocation of R40 will usually follow unless it can be proven that the findings were certainly not relevant for humans.<br>In contrast, R64 as proposed by the RMS is not supported since the reduction in body weight gain in offspring during lactation was confined to a very high dose of 50000 ppm that was also parentally toxic and was not accompanied by a delay in any further developmental landmarks. | |
| (2) | Vol. 3, B.6.1, ADME (Toxicokinetics) | DE: It seems that oral absorption of lenacil in fact will increase with repeated dosing but the oral absorption rate is usually based on the results obtained after single application of a low dose. Unfortunately, the amounts found in bile are not tabulated in the DAR. According to our national evaluation, however, oral absorption following the single low dose will account for about 70 % only. This point should be discussed on the PRAPeR meeting since a change in the view might result in a need for correction of the AOEL. | |

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| 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.6.3.2.1, Oral 90-day toxicity (mouse), B.6.10.3, AOEL | DE: It is difficult to assess whether the effects on blood (in particular leucopenia) im mice at dose levels of 1000 ppm and above are toxicological relevant since a dose response is lacking. The NOAEL is rather seen at 1000 ppm (157 mg/kg bw/d) than at 100 ppm (15.5 mg/kg bw/d). At least, because of this uncertainty and also the wide dose spacing, it is doubtful whether this study may in fact provide the most suitable basis to derive the AOEL. Instead, the 90-day study in rats might be used. | |
| (4) | Vol. 3, B.6.5.1 and B.6.5.2, Long-term toxicity and carcinogenicity in the rat, thyroid tumours | DE: If follicular cell adenoma and carcinoma are combined, the incidence in female rats over the course of the study was 3, 0, 3, and 8 in the control and three dose groups (Table B.6.5.2-1) suggesting a treatment-related effect with a combinded incidence of 16 % at the highest dose level. However, an incidence of 4 top dose females with carcinoma could not be found in the summary of the original study report. The RMS is asked for clarification. | The thyroid is clearly a target organ of lenacil toxicity. In the multi-generation study in rats, a high dose male also exhibited a follicular cell adenoma which can be considered a very rare finding. |
| (5) | Vol. 3, B.6.5.1 and B.6.5.2, Long-term toxicity and carcinogenicity in the rat, mammary tumours | DE: If the combined incidence of mammary adenoma and adenocarcinoma is considered (0, 3, 6, 8), there is evidence for a significant and dose-related increase. However, it must be noticed that a tenfold increase in the dose level produced only a marginal increase in tumour frequency. The relevance of this findings should be discussed on the PRAPeR meeting. | |

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.6.10.1, ADI | DE: A slightly lower ADI of 0.12 mg/kg bw instead of 0.14 mg/kg bw is proposed.<br>The RMS proposal is agreed to derive the ADI from the NOAEL in the long-term study in rats. However, the numeric value is usually set on the basis of the lower mean dietary intake if there is a difference between sexes. For lenacil, this was 12 mg/kg bw/d in male animals. | |
| (7) | Vol. 3, B.6.10.3, AOEL | DE: A somewhat higher systemic AOEL of 0.3 mg/kg bw/d instead of 0.16 mg/kg bw/d is suggested.<br>On one hand, the NOAEL in the 90-day study in mice is not considered an appropriate basis (see comment above). Instead, the AOEL should be derived from the NOAEL in the 90-day rat study (40.6 mg/kg bw/d) that is nearly equal to the NOAEL in the 90-day dog study (44 mg/kg bw/d). If, furthermore, an oral absorption rate of only 70 % is assumed (see comment above), a rounded figure of 0.3 mg/kg bw/d would result. | |

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 |
|---|---|---|---|
| (8) | Vol. 3, B.6.12,<br>Dermal absorption | DE: For the concentrate, 1 % dermal absorption should be assumed whereas the more appropriate value for the dilution might be 16 %. The approach taken by the RMS to include the amount retained in skin is supported. However, if it is possible to distinguish between different layers of *stratum corneum* because values for individual tape strips are given, the first strips (1 and 2) may be excluded also in an *in vitro* study on human skin since it is very unlikely that this material on the surface would become available under *in vivo* conditions. This would give lower values than proposed by the RMS but much higher percentages than suggested by the notifier. | |
| (9) | Volume 3, B.6.15,<br>Exposure data | DE: Exposure data should be recalculated with the proposed AOEL and the proposed dermal absorption [see comment 7 and 8]. | |
| (10) | Volume 3, B.6.15.4,<br>Estimation of worker exposure | DE: It cannot be excluded that re-entry is necessary soon after application e.g. for irrigation or monitoring purposes. Therefore, a quantitative assessment of re-entry exposure should be given. | |

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section 3 - Residues (B.7)

**8. 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, Metabolism, distribution and expression of residues of lenacil in Sugar Beets | DE: We suggest to change the reported harvest intervals (refer to days after last, not first application). Tabular presentations and the text should be amended accordingly. | |
| (2) | Vol. 1, List of End points, summary of residue data (p. 49)<br>Vol. 3, B.7.6.1, Residues resulting from supervised trials | DE: Samples from 4 trials (referenced as F-95-001-RES) were stored for 26 months, but storage stability for lenacil was only documented for a period of 8.5 months. Therefore, the corresponding data should not be used for the MRL calculation and should not be underlined in the residue tables. Tabular presentations and the text should be amended accordingly. | |
| (3) | Vol. 1, List of End points (p. 50),<br>Vol. 3, B.7.11, Estimates of the potential and actual exposure through diet and other means | DE: The acceptability of the chronic intake by consumers should be recalculated with the proposed ADI of 0.12 mg/kg bw [see comments to mammalian toxicology (6)]. | |

**9. 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) | B.8.1.2, Rate of degradation (Annex IIA 7.1.1.2.1, Annex IIIA 9.1.1.1.1),<br>B.8.1.2.1, Aerobic degradation,<br>Derivation of the $DT_{50}$ soil used for the PEC calculations (p. 16) | DE: The study by Berg (1994a) was conducted at pF 2.5 (see page 6) and consequently no correction factor for water content is needed for the three soils (Hillsdale, Sassafras, Tama).<br>The study by Theis (2003) presents as measured MWHC a water content of 51 ±4 Grav.-% (see page 2). Since the study was performed at 40 % of MWHC the water content was 51 %*0.40 during the study and not 27 %*0.40 (see page 16). The correct water content during the study was 20.4 Grav.-% which is wetter than the FOCUS default of 19 %. Consequently no correction factor for water content is needed for the soil (Speyer 2.2).<br>The study by Girkin (2003) presents for each of the four soils both, a measured water content for MWHC (0 bar) and for the matric potential (1/3 bar). Consequently no FOCUS default values must be used. (1) for water content at reference condition pF 2: values at 1/3 bar can be used directly. (2) for water content of the study: the values for on page 16 are not correct and the values from page 8 should be used: Wolston 54.44 %*0.40 = 22.2 Grav.-%; Wick 37.9 %*0.40 = 15.2 Grav.-%; Whimple 77.46 %*0.40 = 31.0 Grav.-%; Sheringham 39.46 %*0.40 =15.8 Grav.-%. Since all four | |

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| 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 |
|---|---|---|---|
| | | soils have been wetter than at reference condition no correction factor for water content is needed. | |
| (2) | B.8.1.2, Rate of degradation (Annex IIA 7.1.1.2.1; Annex IIIA 9.1.1.1.1),<br>B.8.1.2.1, Aerobic degradation | DE: Experts at PRAPeR to discuss whether to include or to exclude the studies from Berg (1994a) from risk assessment. | |
| (3) | B.8.1.2, Rate of degradation (Annex IIA 7.1.1.2.1; Annex IIIA 9.1.1.1.1),<br>B.8.1.2.1, Aerobic degradation | DE: RMS to consider if the study Belasco, J.: Microbial Degradation of 2-$^{14}$C-Lenacil in soil, Document No. LLME-2-79, 1979 would add valid information concerning lenacil or metabolites of lenacil. | |
| (4) | p.17 ff.: Metabolites IN-KF313 and IN-KE121 | DE: Please check the correction factor for water content (see our comment (1)) and use the measured values from the study. | |
| (5) | B.8.1.3, Field studies (Annex IIA 7.1.1.2.2; Annex IIIA 9.1.1.2),<br>B.8.1.3.1, Soil dissipation testing | DE: Please provide information on the kinetical model used (SFO ??) and the assessment of goodness of fit (see FOCUS deg.Kin. 2006 page 80 ff.). The two German sites show a large p-value which could indicate that the model used is not appropriate and a different kinetic model should be used. | |

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) | B.8.1.3, Field studies (Annex IIA 7.1.1.2.2; Annex IIIA 9.1.1.2),<br>B.8.1.3.1, Soil dissipation testing | DE: RMS to check if the study Brodsky, J.: Determination of Residues of Lenacil in Soil, treated with Venzar, season 1989, BE-A-11-90-10-BF, 1990 should be considered. | |
| (7) | B.8.2, Adsorption, desorption and mobility in soil (Annex IIA 7.1.2 and 7.1.3; Annex IIIA 9.1.2),<br>B.8.2.1, Adsorption and desorption of the active substance and relevant metabolites (Annex IIA 7.1.2),<br>Batch Equilibrium (Adsorption/Desorption) Study with IN-KF313 (Berg, D. S., 1996c) | DE: The metabolite IN-KF313 shows no correlation between Kf and OC-content but does show correlation between Kf and all three: pH, CEC and clay content. Please use worst case assumptions such as 10th percentile of 218 in the risk assessment. | |

**10. 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.9.2.12, Effects on primary productivity and macrophyte biomass in field-based microcosms, B.9.2.16, Exposure and risk assessment for aquatic organisms | DE: We agree with the use of a NOEAEC of 22.1 µg as/L from the microcosm study by Jenkins (2005) for risk assessment. However an assessment factor of 3 as proposed by the RMS cannot be supported. We would propose the use of an assessment factor of five instead (see argumentation in column 3). The outcome of the risk assessment would change for 4 x 0.125 kg as/ha but risk would still be manageable by slight risk mitigation measures. | Studies of the effects of the formulation Venzar 80WP on populations of macrophytes, phyto- and zooplankton have been conducted in outdoor ditch microcosms. The applied nominal concentrations were 0.4; 1.53; 5.81; 22.1 and 83.7 µg as/L and the duration of the exposure was 98 days.<br>The $DT_{50}$ of lenacil in the microcosm is between 9.2 d and 12.3 d and in the laboratory study between 29.3 and 66.3 d. The $DT_{90}$ of lenacil in the microcosm is between 30.7 d and 41.0 d and in the laboratory study between 97.2 and 200 d. Concentration of lenacil in the water column reached a peak three days after application, ranging from 29 % of nominal at the lowest treatment group to 58 % of nominal at the highest. The measured levels of lenacil were Day 0: 35 %; Day 3: 46 %; Day 7: 35 %; Day 14: 22 %; Day 28: 6 %; Day 49: 3 %. The microcosms demonstrate not a worst case. The concentration of lenacil could be higher in waterbodies with not so much macrophytes.<br>Analysis of phytoplankton abundance and diversity during the establishment phase was not undertaken. During this period, the water in the microcosms was replaced on a number of occasions, initially to improve the clarity of the water and then to remove algal blooms that occurred in a number of the microcosms. Only those samples taken on Day -1, when the water in the microcosms had stabilised, were analysed.<br>The number of algal cells decreased between Day -1 and Day 7 in control and treated microcosms. In the control microcosms averaged from 604 to 83 $*10^4$ cells /mL. Using Principal Response curve analysis, algal population were affected in all treatment groups between Day 7 and 28 but this was only statistically significant at 83.7 µg as/L on Days 28 and 42. Based on this result |

| 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 |
|---|---|---|---|
| | | | the NOEC community was 22.1 µg as/L. But the number of algal cells was low and the variability between replicate microcosms was high, so the result was considered to be uncertain and a high assessment factor is needed. Recovery can not be detected because the algal number is low over the whole study time. Lenacil has been found to be most toxic to the macrophyte *Elodea* with an NOEC of 5.81 µg as/L and recovery from Day 70. But recovery was observed in October, when the plants started to decrease. |

## 11. 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 B.2.2.15<br>Stability after storage for 14 days at 54°C | FR considers that this study is required to assure if the plant protection product is stable at 54°C. Even if a shelf life study is provided as maximal temperature reached during this study was 31°C, no data are provided on the stability at higher temperature. | If the formulation is not stable at 54°C, FR thinks that an advice has to be added on the label. |
| (2) | Vol.3 B.2.2.22<br>Suspensibility | FR : Please RMS clarify why the suspensibility has been realized and accepted at 0.5 g a.s / L while the minimal recommended concentration is 0.3 g a.s / L. | |
| (3) | LOEP<br>Appearance | FR : In the Vol. 3 B.2.1.7, purity of 99% is for PGAI which is described as a liquid, please RMS clarify if the appearance listing in the LOEP is this of the technical substance and so corrected by 98.6% | |
| (4) | LOEP<br>Partition coefficient | FR : For better comprehensibility, please RMS homogenise result at pH 7 : “1.69” in the LOEP and “1.70” in Vol 3 B.2.1.13 | |
| (5) | Vol.3 B.5.1.1<br>Method Hansen, 1998 – Report No. AMR 3747-96) | FR : Please RMS clarify why the linearity of this method is accepted while only 3 standard solutions were used. | |
| (6) | Vol.3 B.5.5.3<br>Table B.5.5.3-1 Summary of analytical methods(residue) for soil, water and air | FR thinks that method *Brodsky and Zietz, 1990* can not be considered as fully validated on the range from 0.05 to 2.55 mg/kg as only two samples were analysed at 2.55 mg/kg. | |
| (7) | Vol. 4 annex C.1.2.4<br>Methods of analytical for the determination of impurities<br>(Wittig, 2000 – Report No. PR00/015) | FR thinks that analytical method using ICP-OES has to be validated as other method. Even if it is a well-established technique, validation data have to be provided. | |

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

| No. | Column 1<br>Reference to draft assessment report *| Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (8) | Vol.3 Annex C.1.2.4<br>Methods of analytical for the determination of impurities<br>(Hansen, 1998 – Report No. AMR 3747-96) | FR : A typo is appeared in the table. For linearity , only concentration range are reported in the table not $r^2$ while the column is described as “Linearity $r^2$ (conc. Range)” | |
| (9) | Vol.3 Annex C.1.2.4<br>Methods of analytical for the determination of impurities<br>(Hansen, 1998 – Report No. AMR 3747-96) | FR : According to the doc SANCO 3030/099 rev.4, LOQ has to be determined as the lowest concentration tested, at which an acceptable mean recovery with an acceptable RSD is obtained. In this part, LOQ is defined in function of ratio S/N, please RMS clarify. | |

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## 12. 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) | **B.6.6.1 Two generation reproductive toxicity in the rat (Annex IIA 5.6.1)** | FR: agrees with the RMS that the reduction of weight gain in F1 and F2 offsprings during lactation should be considered as adverse; however a labelling with R64 should be accompanied by a labelling with, at least, an R63 phrase. | |
| (2) | **General comment** | FR: in the short and long term studies, lenacil caused various alterations –sometimes dose related- of the thyroid gland in rats as well as in dogs. As stressed by the RMS, as the mechanism has not been clearly elucidated, these effects should be considered relevant for humans. | |

section 3 - Residues (B.7)

### 13. 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, B7.3, Definition of the residue in animal, p7<br>AND<br>Vol.3, B7.8.2 Livestock feeding studies in lactating cows or goats, p 17 | FR: According to results of the dietary burden calculation, animal intake is above the trigger value: 0.135 mg/kg diet (dry weight basis) for beef cattle and 0.12 for pig.<br><br>According to guidelines 7030/VI/95 rev3 and 7031/VI/95 rev4, a livestock metabolism and a feeding study- should be required. | |
| (2) | Vol.3, B7.6.1 Residues resulting from supervised trials, p13 | FR: Only three trials have been performed in southern Europe. According to guideline 7029/VI/95 rev5, a complementary trial should be submitted for sugar beet. | |
| (3) | Vol3.B7.9 Residues in succeeding or rotational crops, p17 | FR: Arguments justifying the non requirement of succeeding and rotational crop study is acceptable only for rotational crop.<br><br>In case of “growth problem”, this argument is no more acceptable because the substitution crop will be sown/planted in a shorter interval. Moreover, it appears that residues are detected in sugar beet leaves (0.04 mg/kg), so attention should be focused on potentially succeeding leafy crops. | |

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### 14. 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, p 17<br>Summary and assessment of studies on route and rate of degradation in soil – rate of degradation | FR : Please, could you explain why the max field DT50 was not retained for the calculation of PECsoil for lenacil whereas the field dissipation study was considered acceptable. | |
| (2) | Vol. 3, B.8, p 17 Table B.8.1.2.1-13<br>Summary and assessment of studies on route and rate of degradation in soil – rate of degradation | FR : Please, could you explain how the DT50 and kinetic fraction of IN-KF121 were calculated ? In the study of Theis (2003, speyer 2.2 soil) M14.0 and M15.0 are considered both to be IN-KF121. As a consequence, M14 and M15 should be added for the kinetic calculations. Could you please confirm if it was done are not ? | |
| (3) | Vol. 3, B.8.1.3, p 21<br>Conclusions of the Field studies | FR: the RMS considered that the DT50 of 88 days can be considered as an outlier because the experiment was characterized hot soil temperature and almost no precipitation. These climatic conditions do not seem extreme for Spain and Southern Europe and have not to be considered as outlier. 26-31°C for soils seem to be reasonable for late spring-summer and 3 months with very low precipitation do not seem surprising. To consider such data as outlier, it should be explicitly compared to typical data. As a consequence, the DT50 of 88 days should be considered valid and should be used for risk assessment (PECsoil calculation at least). | |
| (4) | Vol.3, B.8, p22<br>Adsoprtion/desorption studies | FR : Please, could you indicate if the preliminary test to determine the adsorption of the test substance on the surface of the test vessels was carried out and what the results were. | |

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 |
|---|---|---|---|
| (5) | Vol.3, B.8, p24, Table B.8.2.1-5<br>Adsoprtion/desorption study | FR : In the adsorption study of IN-KF313 (Berg, 1996), the pH values lay in the small range of 6.3 to 6.8. Additionally, the Sassafras soil and the Hillsdale soil are very similar in texture, OC and CEC. We do not believe that these two soils should be considered different. Finally, the Kfoc values obtained for Tama (79 l/kg) and the values obtained for Sassafras and Hillsdale (823.8 and 769 l/kg) suggest that there may be a dependence of the adsorption to one soil parameter. However, with only 2 real different soils, such relation can only be suspected. We think that additional adsorption data are needed. | |
| (6) | Vol.3, B.8, p 31<br>PECsoil | FR : PECsoil metabolites were calculated with formation fraction and not with maximal measured percentage in soil. This is not the recommended approach but can be considered as conservative for risk assessment. | |
| (7) | Vol.3, B.8, p 44 Table B.8.6.1-1<br>PECgw | FR : The water solubility of metabolites were defined by EPIWIN estimation and not with a laboratory study. | |
| (8) | Vol.3, B.8, p 44 Table B.8.6.1-1<br>PECgw, PECsw | FR: The geomean DT50 of the total system was applied to the sediment phase and a DT50 of 1000 days was used for the water phase as default value. From the experimental data (Table B.8.4.4-2 and B.8.4.4-3), the opposite might be also possible (i.e., degradation of lenacil happened in the water phase). It may be worthwhile to additionally calculate PECsw and PECsed with this option to evaluate the impact on the aquatic risk assessment. | |
| (9) | Vol.3, B.8, p 67<br>PECsw | FR : A step 4 to refine the aquatic assessment for drift should be carried out. See the ecotox comment 5(6). | |

### 15. 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.9.1.2, Avian dietary toxicity test | FR: It would have been easier to agree with the RMS conclusion if the abstract of the study would have been more detailed, especially concerning the weight of birds. | |
| (2) | Vol.3, B.9.2.8, Effects on algae | FR: It would have been more convenient to read the results of algae tests if they would have been presented in tables, instead of text. | |
| (3) | Vol.3, B.9.2.8, Test on *P. subcapitata*, page 9-18 | FR: In the study from Douglas and Handley (1988), is the ErC50 really measured between 24 and 48 hours ? Why is it not calculated at 72 hours ?<br><br>As long as no analytical measurement was conducted during the test, this study can not be accepted. It can only be considered as supporting data because it confirms results obtained in other tests. Therefore, values obtained should be deleted form the LoEP in vol.1. | |
| (4) | Vol.3, B.9.2.11, Test on algae with the preparation, page 9-22 | FR: As long as no analytical measurement was conducted during the test, this study can not be accepted. It can only be considered as supporting data because it confirms results obtained in other tests. Moreover, toxicity is in the same range as of the active substance itself. Therefore, values obtained should be deleted form the LoEP in vol.1. | |

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 |
|---|---|---|---|
| (5) | Vol.3, B.9.2.12, Microcosm study (Jenkins, 2005) | FR: We have several comments on this study:<br>- PRC: the NOAEC proposed can not be retained because a recovery was observed for phytoplankton after 8 weeks, when lenacil can be applied up to 4 times a year with a maximum interval of 14 days. Only the NOEC of 22.1 µg a.s./L can be considered.<br>- Concentrations: as long as initial measured concentrations were much lower than the nominal, even 3 hours after treatment, the endpoints have to be based on these initial measured concentrations, and not on the nominal ones.<br>- General NOAEC: two species are more sensitive than the proposed NOAEC: Elodea Canadensis (NOEC = 5.81 µg a.s./L) and Charophyta (NOEC < 0.4 µg a.s./L), both expressed as nominal concentrations. Due to the very high sensitivity of Charophyta, and because only one treatment was applied to the microcosm, a global NOAEC can not ignore effects observed on these taxa. We then propose to use a NOEC based on the measured concentration of the lowest nominal one, i.e. 0.13 µg a.s./L. | |

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 |
|---|---|---|---|
| (6) | Vol.3, B.9.2.16, Risk assessment for aquatic organisms, Point 5 Risk refinement for algae and plants | FR: Considering our previous comment, we propose to assess the refined risk to algae and aquatic plants using a NOEC of 0.13 µ a.s./L.<br>The trigger value could be 3, as proposed by the RMS, because of the uncertainty on possible effects on these species that could occur after 4 treatments with 14 days interval and which are not covered by this study.<br>With this endpoint modification, it is quite sure that there will be a need for further refinement of the risk assessment for algae and aquatic plants using Focus step 4 calculations. | |
| (7) | Vol.3, B.9.6.4, Subchronic effects on earthworms | FR: It is surprising that the effect on earthworm reproduction at the application rate of 32 kg a.s./ha is not significantly different from the control, with an inhibition of reproduction around 20%. There is no information in the text about the statistical test used in this study. Could the RMS complete the abstract and confirm that an inhibition of reproduction of 20% is not significant ? This has to be checked also for the other application rates, as a dose-response is not clear in this test. | |
| (8) | Vol.1, LoEP, Effects on algae | FR: The first test on *P. subcapitata* was conducted during 96h, but the endpoints are reported for 72h. This should be mentioned in the table. | |
| (9) | Vol.1, LoEP, Effects on algae | FR: As long as the second test on *P. subcapitata* is not valid (see comment no 5(3)), the results should be removed from the LoEP. | |

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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, LoEP, Effects on algae | FR: As long as the test on *P. subcapitata* with the preparation is not valid (see comment no 5(4)), the results should be removed from the LoEP. | |
| (11) | Vol.1, LoEP, Microcosm study | FR: Considering comments no 5(5) and 5(6), the endpoint related to the microcosm study and the risk assessment for algae and aquatic plants should be modified. | |

**16. 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 4 C.1.1, manufacturing process | UK: Reaction time and temperature should be provided for the method of manufacture. | |
| (2) | Vol 4 C.1.1, manufacturing process | UK: Full discussion of the source of the impurities found in the technical material should be provided. | |
| (3) | Vol 4, C.1.2.3, analytical profile of batches | UK: Compound 4, 7 and 8 have been listed in the 5 batch analysis but stated to be not analysed. It is unclear if this means the impurities have been sought but not found or not sought. | |
| (4) | Vol 4, C.1.2.3, analytical profile of batches | UK: Analytical closure should not include those impurities which were quantified as <1 g/kg. | |
| (5) | Vol 4, C.1.2.3, analytical profile of batches | UK: Compound 9; If the values in the 5 batch analysis data have been quantified as total sulphur, this is how the values should be presented and utilised in the calculation of analytical closure. | |
| (6) | Vol 4, C.1.2.3, analytical profile of batches | UK: It appears that several starting materials and intermediates have not been sought in the 5 batch analysis (see also comment at Vol 4 C .1.1.). | |
| (7) | Vol 4, C.1.2.3, analytical profile of batches | UK: Compound 11 has been sought in the 5 batch analysis data presented in Table C.1.2.3-3 but not in Table C.1.2.3-1, although the notifier states that the data provided in Table C.1.2.3-2 and C.1.2.3-3 are not relevant it should be clarified if this impurity is no longer considered likely (see also comment at Vol 4 C .1.1.). | |

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

| No. | Column 1<br>Reference to draft assessment report * | Column 2<br>Comment * (restricted to 500 characters, ca.10 lines) | Column 3<br>Further explanations |
|---|---|---|---|
| (8) | Vol 4, C.1.2.3, analytical profile of batches | UK: The analytical profile of tox batches has not been provided. | |
| (9) | Vol 4, C.1.2.3, analytical profile of batches | UK: Water content in Table C.1.2.3-1 has been measured by loss on drying and therefore the method used is not specific | |

section 2 - Mammalian toxicology (B.6)

**17. 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 4, C.1.2.3, batches used in toxicity testing | UK: In the absence of specific details, we would like to have assurance that the material used in the toxicity testing was produced using the same manufacturing method as used in the full production plants (therefore likely to have a similar impurity profile) rather than in a small lab based system. | |
| (2) | Vol 3, B.6.1, Absorption, distribution, excretion and metabolism | UK: Does the RMS consider that the increased absorption seen following repeat low dosing is a result of an increase in the activity of gut micro flora? | |
| (3) | Vol 3, B.6.3, Short term toxicity | UK: The mouse is clearly the most sensitive species, rat and dog similar | |
| (4) | Vol 3, B.6.4.1.3, In vitro mammalian cytogenetics | UK: More details are required on the positive findings in chromosome aberration test. From the table it appears that the aberrations did not include any gaps it would be useful to know if there was any increase in a single aberration or a spectrum. | |

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 |
|---|---|---|---|
| (5) | Vol 3, B.6.5, carcinogenicity | UK: We agree with the RMS conclusions on the tumours apart from the lung tumours in the mouse. The only two Historical Control groups did not have any carcinomas and the 7000 ppm males were well over the Historical Control value for the combined incidence. It would have been useful to have the incidence for lung tumours for all groups from the 2 studies from which the Historical Control data have been derived (assuming the test compounds didn't cause lung tumours!). Overall based on the data presented the tumours should be considered as treatment related rather than „equivocal toxicological significance', and consider the need for Cat 3 classification. | |
| (6) | Vol 3, B.6.6.3, reproductive toxicity | UK: In the absence of a lactating goat study we agree with R64 classification | |
| (7) | Vol 3, B.6.8.1, toxicity of metabolites | UK: Provided the levels of metabolites are low compared to parent we are content with the RMS assessment. Therefore it would be useful if levels (for both impurities and parent) were given (in plants and potential for groundwater). | |
| (8) | Vol 3, B.6.10.1, 6.10.2 and 6.10.3, reference values | UK: The reference values proposed are acceptable. | |

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, B.6.12, dermal absorption | UK: The dermal absorption section could be more transparent. The RMS firstly states that a dermal absorption rate of 2.7% for the concentrate and of 34.2% for the diluted formulation can be derived based on treated skin plus receptor fluid in line with SANCO/222/2000 rev. 7 Guidance. They then go on to indicate that you can exclude the first couple of tape strips. They state that the exclusion of stratum corneum values from total absorption is in accordance with recommendations from the Standing Committees on Plants (2002) and Cosmetics (2003). And give a lower set of values, not very clearly laid out. But the RMS OpEx calculations use 2.7 and 34.2%. Overall UK would be happy to exclude the first couple of tape strips to give values of 0.88 and 15.5% (high and low doses). | |
| (10) | Vol. 3, B.6.15.3<br>Estimation of bystander exposure | UK: The bystander exposure estimate uses a dermal absorption value of 0.4% (the value proposed by the notifier) rather than 34.2% (the value used by the RMS in the operator exposure estimates). | |
| (11) | Vol. 3, B.6.15.4,<br>Estimation of worker exposure | UK: As „Venzar 80 WP' is applied as a post-emergence treatment (BBCH 10-31), it is possible that workers inspecting a treated crop may be exposed to dislodgeable foliar residues of lenacil. It is, therefore, considered appropriate to evaluate worker exposure (taking into account the maximum total dose). | |

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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, Annex B ‚Appendix: estimation of the exposure' | UK: It is noted that the both exposure estimates using the UK POEM seem to have an error in row 12 („Dermal exposure to formulation'). The value presented here (16.47 mg/day in both estimates) relates to inhalation, rather than dermal, exposure. However, it is noted that this error does not affect the calculation. | |

section 3 - Residues (B.7)

**18. 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.7.2, metabolism in livestock | UK: The requirement for metabolism studies has been compared to animal feed intake on a dry weight basis. This comparison should be made to intake as received. However, it is agreed that animal metabolism data are not required. | |
| (2) | Vol 3, B.7.3, Definition of the residue | UK: It is stated that the critical GAP growth stage was not covered by the metabolism data provided, but that this was considered acceptable. This statement requires further justification. | |
| (3) | Vol 3, B.7.5, identification of critical GAPs | UK: We think there may be a typo. Spray concentration does not agree with application rate and water volumes for use pattern provided in Table B.7.4-1. | |
| (4) | Vol 3, B.7.6 supervised trials | UK: It is not clear from the method details submitted which methods are considered acceptable to support the residue trials. The methods suitability as enforcement methods also appears to have been considered. In addition some of the methods have also been considered in B5. For each of the methods full details of any omissions in the validation data should be provided and a conclusion on the acceptability of the method for pre-registration purposes. In addition it should be made clear if any of the residue trial data cannot be accepted due to the absence of supporting method validation data. | |

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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.7.6.1 residues resulting from supervised trials | UK: Several residue trials have been considered acceptable with an earlier growth stage than indicated by the critical GAP. | |
| (6) | Vol 3, B.7.9, residues in succeeding or rotational crops | UK: The information provided is not sufficient to conclude that less than 10% of the active substance would be present after 30 days. The RMS has indicated that due to the long interval between application and harvest the information is sufficient, however this does not address plant back after crop failure | |
| (7) | Vol 3, B.7.14, storage stability of residue samples | UK: Additional storage stability data are required to support the residue trials in which samples were stored for 26 months. | |

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

**19. 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, field studies and LoEP | UK: There seems to be some inconsistency with DT50s listed for the field studies: values of 23 – 110 days listed in LoEP, whereas values of 18 – 88 days quoted in Vol 3. | |
| (2) | Vol 3 B.8.1.2.1, aerobic degradation in 3 soils | UK: The study by Berg (1994b) has been deemed invalid due to saturation of microbial processes. However, we consider that some evidence of this should be presented e.g. a range-finding study before the (longer) DT50s from this study are dismissed. | |
| (3) | Vol 3 B.8.3, B.8.6, PEC in soil, groundwater and surface water (and LoEP) | UK: It is unclear why DT50s from field studies were not considered for use as input values for PECs, PECsw and PECgw. | |
| (4) | Vol 3 B.8.3, B.8.6, PEC in soil, groundwater and surface water (and LoEP) | UK: We consider that the chosen DT50 value of 9.9 days may under-estimate the degradation time for lenacil hence potentially under-estimating PECs, PECsw and PECgw | |

section 5 - Ecotoxicology (B.9)

**20. 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.9.2.16, risk assessment for aquatic organisms | UK: the acute and chronic risk to fish and aquatic invertebrates is acceptable; there is a potentially high risk to algae and aquatic plants and all first tier TERs at FOCUS Step 3 are below the appropriate Annex VI trigger value. It is noted that higher tier data that assessed the impact of lenacil on algae and aquatic plants has been submitted and assessed. One study assessed the impact of lenacil on macrophyte biomass following simulated spray drift contamination. The other study assessed the impact on primary productivity and macrophyte biomass in a microcosm. It would appear that on the basis of these data the proposed endpoint is 22.1 ug/l and that an uncertainty factor of 3 is proposed, resulting in a regulatory concentration of 7.4 ug/l. On this basis „safe' uses can be predicted in relevant scenarios. At the proposed endpoint of 22.1 ug/L it is noted that there were effects on Elodea and Charophyta in the microcosm study, whilst the NOEC for Elodea from the spray drift study was 10 ug/L. On this basis, it is questioned whether the endpoint is sufficiently protective for Elodea. It is proposed that these two studies should be discussed at an Expert meeting. | |

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

**21. 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, 1.3.1 name and address applicant | NL: Schirm has taken over (the dossier from) DuPont? It is kind of confusing to see references being made to a dossier submitted by DuPont while the applicant is Schirm. | |
| 2. | Vol 1, LOEP, log Pow | NL: The value at pH 7 is not consistent with the value in volume 3 (1.70 and 1.69). | |
| 3. | Vol 1, level 4, 4.2, ppp data | NL: NL agrees with the RMS that this data can be handled at MS level. | |
| 4. | Vol 1, level 4, 4.5, RAM for plant material | NL: Either more data is required or not. It is unclear what the RMS wants the notifier to do. | |
| 5. | Vol 3, B.2.2.19, shelf-life | NL: The summary suggests the product was stored in paper only, while in B.3 the cardboard box appears to be sealed or laminated with LDPE. Is the assumption that the same packaging as described in B3 was used correct? | |
| 6. | Vol 3, B.2.2.22, suspensibility | NL: Was suspensibility determined analytically or gravimetrically? It seems a sprayability test will be required (at MS level?). | |
| 7. | Vol 3, table B.2.2.-2, shelf life results | NL: Change of properties does not seem shocking – properties do not change dramatically. The variance in results seem to be within acceptable limits. NL would probably be content with a sprayability test as the suspensibility is too low and wetting is too slow. | |
| 8. | Vol 3, B.3.5.1.1, table B.3.5.1.1.-1 | NL: No. 3 under material/bag mentions a HDPE film of 20 „my'? What are „my'? Micrometers? | |

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

| No. | Column 1<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, B.5.3.2, RAM for water | NL: In general, NL does not consider DAD as highly specific. At below 230 nm UV spectra are never specific and therefore the identity is insufficiently confirmed using the wavelengths mentioned. NL believes a confirmatory method is required. | |
| 10 | Vol 4, table C.1.2.3-2, comments below table | NL: If a concentration is below the LOQ („less than' values), then it cannot be taken into account for the analytical closure. | |

section 2 - Mammalian toxicology (B.6)

**22. 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. | | | |

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section 3 - Residues (B.7)

**23. 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: Please further clarify why IN-KC943 is considered non-toxicologically relevant. For example: better soluble and probably fast excreted. | |

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

**24. 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, level 2, Chapter 2.5 | NL: Max field DT50 is to be used for PECsoil. After leaving out the Spanish trial (DT50 88 days), this is the DT50 of French trial of 52 days. Check interval for multiple appl.<br>lysimeter application may not be worst-case (this could be a single application of 500 g a.s./ha)<br>NL: w/s: stated that only 1 major metabolite occurred, M20.5 (=IN-KF313). Later on also M15 is mentioned, which also seems to be major. Maybe just the phrasing needs revision (since from B8 only IN-KF313 appears to be major). | |
| 2 | Vol. 1 level 3 proposed decision | NL: In principle agreed but see comments on lysimeter study. | |
| 3 | Vol. 1 level 4 data requirements | NL: More data on unidentified lysimeter metabolites are considered necessary (either fate – e.g., substance properties- or ecotox data – e.g., toxicity studies with lysimeter leachates) | |

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 |
|---|---|---|---|
| 4 | Vol. 1 level 2 LoEP | NL: Route of degradation: please state temperature of study also for max. formed metabolites.<br>Rate of degradation (lab): please indicate soil type (i.e. texture) in designated column for soil type, not (only) location.<br>DT50 field non-normalised range from 23-110 days, while in Vol. 1 level 2 a DT50 field of 18-88 is mentioned. Were these normalised? If so then why does LoEP state that normalisation is not done.<br>PECsoil: we disagree with the chosen max DT50 lab, instead non-normalised max field (52 days when Spanish trial is considered outlier) should be used. This does not affect the initial PEC for the single application, however (but does affect all other PECs). So, if this is the PEC used for TER calculation then the ecotox RA does not change.<br>Both metabolites are given the same molecular weight ((boxes method of calculation), this appears to be unlikely, please check. See also box PECsw/sed.<br>PECsw/sed: the (geo)mean DT50system should have been used for the sediment compartment (instead of worst-case). RA is conservative and acceptable.<br>PECgw: in Vol 1 it is stated that calculations were based on arithmetic mean DT50 values, in LoEP it states geomean (for the same values). Please mind consistency. | |

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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 |
|---|---|---|---|
| 5 | Vol. 3, B.8.1.1.1 and 8.1.2.1 (route and rate of degradation in soil) | NL: USA soils discarded partly because of high application rates, this explanation alone is not enough to leave these soils out, since for the 10 C study also a high application rate was used. So only the poor storage can be used as reason to discard these USA soils. Alternatively a remark could be made about the high application rate in the 10 C study.<br>Comparison of lab and field DT50 values (page 8-16 and 8-17) (argumentation for use of lab values also for PECsoil) is not based on values given in LoEP. From the LoEP it appears that a value of 52 days should be used for PECsoil calculations (see remark (5)). Please check consistency.<br>Degradation scheme (p 8-19) does not seem complete (major IN-KE 121 not presented). | |
| 6 | Vol. 3, B.8.2.4 Lysimeter studies | NL: Although efforts have already been made to identify M1, M2 and M3, we still think that more information is required, since these metabolites (or molecule fragments) show a high potential for leaching. | |

section 5 - Ecotoxicology (B.9)

**25. 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 | B.9.1.8, Summary of effects on birds | NL: In the first sentence below table B.9.1.8-1 is mentioned: "The risk assessment for mammals….". „Mammals' should be „birds'. | |
| 2 | B.9.1.8, Summary of effects on birds | NL: In table B.9.1.8-3 are a few mistakes:<br>- „mall' should be „small';<br>- no value for ftwa should be mentioned for the long-term exposure because it concerns insects (in the table a value of 0.53 is mentioned). The value of the ETE is right. | |
| 3 | B.9.2.12 Microcosm and mesocosm study | NL: It is concluded by the RMS that the overall NOAEC = 22.1 µg as/L, covering most of the species examined.<br>NL does not agree with this endpoint. All species must be covered. The NOEAEC for *Elodea Canadensis* was 5.81 µg as/L. Significant, immediate impact on abundance and health was evident at the two higher treatments on days 7 and 14, without recovery within 8 weeks. Hence, NL is of the opinion that the NOEAEC of 5.81 µg as/L should be a better endpoint of the mesocosm study. However, the NOEC for *Charophyta* is even lower than the lowest dose (< 0.4 µg as/L). This is simply ignored by the RMS. Are there explanations why this species seems to be so sensitive? Dependent on the explanation this can lead to an even lower endpoint of the mesocosm study. | |

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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 |
|---|---|---|---|
| 4 | B.9.2.16 Exposure and risk assessment for aquatic organisms | NL: Default crop relevant buffer distances are mentioned for ditches, streams and ponds. If these are the standard buffer zones in the FOCUS scenarios they don't have to be mentioned here explicitly. | |
| 5 | B.9.2.16 Exposure and risk assessment for aquatic organisms; 4-Risk assessment for aquatic plants | NL: As already stated NL is of the opinion that the NOEAEC of 5.81 µg as/L is a better endpoint of the mesocosm study. But then the effects at even the lowest dose for *Charophyta* must be explained in a sufficient way. Normally a safety factor of 3 is applied on the NOEAEC. But dependent on the explanation regarding the effects on *Charophyta* the endpoint may be even lower. It may be important to compare the FOCUS exposure profile with the toxicity profile, as described in a publication of Boesten et al. (Conceptual model for improving the link between exposure and effects in the aquatic risk assessment of pesticides. Ecotoxicology and Environmental safety, 2006) and also discussed in the Elink-workshops. | |
| 6 | B.9.2.16 Exposure and risk assessment for aquatic organisms; 4-Risk assessment for aquatic plants | NL: In the last sentence of this paragraph a buffer zone is mentioned. But this is the default buffer zone for the pond scenario. For the other scenario's different default buffer zones are valid. If it are just default buffer zones it is not necessary to mention them here explicitly. | |

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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 | B.9.4.8 Exposure and risk assessment for bees | NL: In the last sentence it is mentioned that sugar/fodder beets are non-flowering crops. This is true, but it is no argument for low risk to bees, because flowering weeds may also be an attractive source for bees. | |
| 8 | List of endpoints | NL: Mesocosm test aquatic organisms: the NOEAEC of 5.81 µg as/L for *Elodea Canadensis* is not mentioned in the LoEP. NL does not agree with the NOEAEC of 22.1 µg as/L. All of the species must be covered. See also point 3 and 5 of the afore mentioned comments. | |

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

**26. 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, B.5.3.1 analytical method residues in soil | AT: Method Brodsky and Zietz is not acceptable as primary method since the numbers of replicates are too low. Therefore it should be deleted from the list of endpoints. | |
| (2) | Vol. 3, B.5.3.3 analytical method residues in air | AT: The method is not sensitive enough (LOQ = 0.1 mg/$m^3$) to cover the concentration C (0.048 mg/$m^3$) as required according to guidance document 825/00. A new method/validation must be provided. | |
| (3) | Vol. 4, C.1.2 production plant Raschig | AT: Is plant [redacted] obsolete? If not, details (address etc..), information on production process, current representative batches, and an assessment on equivalence according to guidance document 10597 is required. | |

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section 2 - Mammalian toxicology (B.6)

**27. 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 |
|---|---|---|---|
| | | | |

section 3 - Residues (B.7)

**28. 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 |
|---|---|---|---|
| | | | |

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

**29. 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, aerobic degradation in soil | AT: classification error: soil type in table B.8.1.1.1-1 should be sandy loam and not loamy sand. | |
| (2) | Vol. 3, B.8.1.2, Rate of degradation | AT: Only soils with pH < 7 were chosen | |
| (3) | Vol. 3, B.8.1.2, Rate of degradation | AT: p 8-8. classification errors – the soils types are not in USDA classification system; markings in the table (a and b) have no explanations. | |
| (4) | Vol. 3, B.8.1.2, Rate of degradation, p 8-16, Derivation of the $DT_{50}$ soil used for the PEC calculations | AT: we consider the $DT_{50}$ of 9.9 days an underestimation of the degradation of lenacil. Furthermore, calculations of arithmetic mean based on the 5 european soils did not provide $DT_{50}$ of 9.9 days but of 10.6 days (based on table B.8.1.2.1-12). As well, arithmetic mean calculations of $DT_{50}$ for metabolites were not consistent to the values from the notifier. And as mentioned by RMS, geometrical mean should be used. | |
| (5) | Vol.3, B.8.1.3, Field studies | AT: p 8-21. $DT_{50}$ of 88 days is considered by notifier and RMS as outlier since high soil temperature and low precipitations were recorded during the study. This value should be taken into consideration as worst case since such conditions are not exceptional for southern Europe. | |

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.8.2.1 Adsorption and desorption of the active substance and relevant metabolites | AT: table 8.2.1-3, classification error – the soil types are not in USDA classification system | |
| (7) | Vol.3, B.8.3 Predicted environmental concentration in soil | AT: Worst case from field studies should be used – 88 days, and maximum appearance should be used for metabolites and not the formation fraction. | |

section 5 - Ecotoxicology (B.9)

**30. 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.9.1.8 Summary of effects on birds – exposure and risk assessment for birds<br>Table B.9.1.8-3 | AT: To avoid misunderstandings the $f_{twa}$ of 0.53 which is stated in the table should be deleted as it will not be used to calculate the long-term ETE for insectivorous birds. | |
| (2) | Vol. 3, B.9.2 Effects on aquatic organisms, B.9.2.8 Effects on algae | AT: The study by Douglas M.T. and Handley J.W., 1988 is regarded as not acceptable and should only be used as additional information. Therefore we are of the opinion that the endpoint of this study should not be stated in the LoEP. | |
| (3) | Vol. 3, B.9.2.16 Exposure and risk assessment for aquatic organisms | AT: The risk assessment based on the NOAEC derived from the mesocosm study should be discussed. On the one hand the used NOAEC of 22.1 µg a.s./L should be discussed regarding the effects on *Elodea sp.* (NOEC = 8.51 µg/L) and Charophyta (NOEC < 0.4 µg/L) and on the other hand the safety of factor of 3 should be questioned (regarding missing analysis of abundance and diversity of phytoplankton, application rate and potential of recovery). | |
| (4) | Vol.3, B.9.5.4 Summary of effects, exposure and risk assessment for non-target terrestrial arthropods | AT: The HQ-approach is only validated for *Aphidius rhopalosiphi* and *Typhlodromus pyri*. Therefore, it should not be used for the risk assessment of *Chrysoperla carnea* and *Aleochara bilineata.* | |
| (5) | Vol.1, List of Endpoints, Effects on other | AT: HQ values of *Aleochara bilineata* and *Chrysoperla carnea* should not be listed in the | |

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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 |
|---|---|---|---|
| | arthropod species | LoEP (see above). | |

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

**31. 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. 4, C.1.1. Method of Manufacture p.4 | EFSA: in the description of the synthesis pathway [redacted] is mentioned, however the formula drawn is rather [redacted] which seems to been used in the manufacture. Also the name [redacted] is not the adequate one in the first reaction before acidification | |
| (2) | Vol. 4, C.2.2-2. Identity of isomers, impurities and additives in technical material p.8 | EFSA: information on the level of [redacted] should be given.<br>It was agreed at PRAPeR 06 to require this information due to the fact that the [redacted] level (expressed in moles) can influence the (eco)toxicological as well as the physical and chemical properties of the formulation | |
| (3) | Vol. 4, C.1.2.3-1 Analytical Profile of Batches p.9 | EFSA: the dates of manufacture for the batches should be given | |
| (4) | Vol. 4, C.1.2.3-1 Analytical Profile of Batches p.9 | EFSA: if impurities 4, 7 and 8 were not analysed for in the representative batches, are they included only for the reason that in the other- non representative – batches were analysed for? If so, why impurity 11 is not included, which was analysed for and also detected in the old batches? | |
| (5) | Vol. 1, List of endpoints p.40 | EFSA: instead of not applicable in the fields for melting and boiling point probably would be more correct to write that decomposes above 270$^{o}$C | |

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

| No. | Column 1<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.2.2.15 Stability after storage for 14 days at 54°C p.2-16 | EFSA:The stability of the preparation after storage for 14 days at 54 °C according to the Directive should be provided | |
| (7) | Vol 1, level 4, 4.5, Methods of analysis p.93<br>Vol. 3, B.5.2.1 Analytical method for residues in plants p.5-6 | EFSA is of the opinion that the study Tillkes, 1998 addresses the demonstration of the applicability of DFG S19, even if it the validation does not fully comply with the requirements of guidance document 825/00, as a fully validated method for monitoring in sugar beet is available | |
| (8) | Vol. 3, B.5.3.3 Analytical method for residues in air p.5-11 | EFSA: The LOQ = 0.1 mg/m$^3$ is higher than the concentration C (0.048 mg/m$^3$) required according to guidance document 825/00. A new method/validation must be provided | |

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**section 2: Mammalian toxicology**

**32. . Mammalian Toxicology**

| 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.6.1 Toxicokinetics<br>Oral absorption. Page 3 | EFSA: According to the summary RMS states that "based on urinary excreted radioactivity after a single dose, oral absorption represents 63-82% of administered low dose level" but according to table B.6.1-4 this value correspond to the sum of urine + faeces –parent.<br>Please, could the RMS clarify this point? | |
| (2) | Vol. 3, B.6.1 Toxicokinetics<br>Oral absorption. | EFSA: RMS proposes to take the values of repeated dosing (85%) into account for setting the correction factor for oral absorption based on urinary and faeces excretion considering the metabolites excretion. The inclusion of metabolites excretion as absorbed and the use of the values of repeated dosing for setting the oral absorption should be further discussed. | |
| (3) | Vol. 3, B.6.5. Long-term toxicity and carcinogenicity.<br>Carcinogenic properties | EFSA: With regard to carcinogenicity RMS states that equivocal findings were found in rats (mammary gland tumour) and mice (lung alveolar tumor and hepatocellular adenoma). The carcinogenicity properties should be further discussed based on findings outside the historical control data. | |

**section 2: Mammalian toxicology**

| 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.6.5 Long-term toxicity and carcinogenicity. Historical control data | EFSA: Could the RMS clarify whether the laboratory control data is relevant to the strain used in the long-term studies, also with regard to the date of the study? | |
| (5) | Vol.3, B.6.6. Reproductive toxicity. Proposal for classification. R64. | EFSA: As RMS already mentioned on page 45, the proposal to classify Lenacil as R64 based on decreased body weight in offspring during lactation should be discussed and agreed on. | |
| (6) | Vol. 3, B.6.8.1 Toxicological studies on metabolites. | EFSA: Could the RMS confirm if the metabolites found in various environmental compartments can be considered as the same or less toxicity as Lenacil? | |
| (7) | Vol.3, B.6.12 Dermal absorption. Absorbed dose. | EFSA: RMS considered as absorbed dose the dose in the receptor + skin + dose on tape strips (1-8). Nevertheless, the first two tape strips could be considered as not absorbed since they can be lost by desquamation. | |
| (7) | Vol.3, B.6.15.3 Bystander Exposure. Input values. | EFSA: the input values should be checked since dermal absorption was considered 0.4% when the proposal by RMS was initially 34.2% for the dilution (see B.6.12). In addition, body weight of 60 kg is considered more appropriate. | |
| (9) | Vol. 3, B.6.15.4 Worker Exposure | EFSA: some activities such as inspection could be considered in the worker exposure assessment. | |

**section 2: Mammalian toxicology**

| 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, B6 General | EFSA: Is there any toxicologically relevant difference between the batches produced by [redacted], 1998 and the ones produced by [redacted] also with regard to proposed current specification? | |
| (11) | Vol.3, B6 General | EFSA: Could the RMS clarify whether the batches used in the toxicological studies were in accordance with batches produced by [redacted] 1998 and/or [redacted] 1998 and/or [redacted] 2000? | |

**section 3: Residues**

**33. . Residues**

| 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) | Volume 1, 2.4, Plant metabolism | EFSA: In Volume 1, 2.4 the RMS states: „A non-negligible polar metabolites fraction was also characterized in sugar beet foliage at harvest (37.9 % of TRR; 0.06 mg/kg) but no further tentative characterization/identification was attempted.' It should be clarified if identification/charac-terisation of metabolites was sufficient. | |
| (2) | Vol. 3, B.7.2, Metabolism in livestock | EFSA: Intake calculations provided in the DAR show that for beef cattle and pigs the trigger value (0.1 mg/kg diet dry matter/day) is exceeded. A metabolism study on ruminants is required. A metabolism study on pigs is required if the metabolic patterns differ significantly in the rat as compared to ruminants.<br>See also comment (10), residue trials. | |
| (3) | Vol. 3, B.7.2, Definition of residues | EFSA: The RMS states that the metabolism study is considered as valid despite of the fact that the notified growth stage of application was not covered by the metabolism study. However, the RMS does not provide a justification for this conclusion. | |

**section 3: Residues**

| 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.7.2, Definition of residues | EFSA: In the toxicology section the question was raised if the metabolites found in various environmental compartments can be considered as the same or less toxicity as lenacil. On the basis of the decision concerning IN-KQ961 it should be discussed if this metabolite needs to be included in the residue definitions. | |
| (5) | Vol. 3, B.7.6, Residue trials, analytical methods used | EFSA: From the presentation in the DAR it is not clear which of the analytical methods were used in the following residue trials: Germany 2001: G01N003R-G01N006R, Portugal 2002: P02N001R and Spain 2005: 688479. | |
| (6) | Vol. 3, B.7.6, Residue trials, analytical methods used | EFSA: Analytical method Tillkes, 1998: EFSA agrees to the conclusion of the RMS that the validation data are not complete. However, the validation data for methods used in residue trials should comply with guidance document SANCO/3029/99 concerning methods of analysis in support of pre-registration requirements. | |
| (7) | Vol. 3, B.7.6, Residue trials, analytical methods used | EFSA: Analytical method Hamburger, 2002 and Mende, 2002: Information on some of the parameters (linearity, precision – repeatability) required by guidance document SANCO/3029/99 and the conclusion of the RMS concerning the acceptability of the method are missing. | |

**section 3: Residues**

| 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 |
|---|---|---|---|
| (8) | Vol. 3, B.7.6, Residue trials, analytical methods used | EFSA: Analytical method Witte, 2006: An independent laboratory validation is required for methods used for monitoring but not for methods used in residue trials only. | |
| (9) | Vol. 3, B.7.6, Residue trials | EFSA: Criteria for assessing the validity of the reported supervised trials are not mentioned in the DAR. It is noted that several studies which were not carried out according to the notified cGAP (esp. concerning GS) were accepted and that no full data set for Southern Europe has been submitted. Only few results for residues in leaves from trials carried out according to the cGAP are available and therefore only tentative dietary burden calculations could be carried out. | |
| (10) | Vol. 3, B.7.9, Residues in rotational crops | EFSA: DT90 values of up to 283 days have been found for lenacil in field studies. Therefore significant residues of lenacil in soil have to be expected up to the planting time of rotational crops and the possible uptake of residues in following crops has to be addressed. | |
| (11) | Vol. 3, B.7.10, Re-entry interval, withholding period | EFSA: Residues of up to 19 mg/kg (day 0) have been found in sugar beet leaves after application of lenacil. Therefore, the requirement of a re-entry period and the prohibition of the feeding of sugar beet tops after thinnening and crop failure should be addressed. | |

**section 3: Residues**

| 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, B.7.14, Storage stability of residue samples | EFSA: In the residue trials samples have been stored frozen for up to 26 months. Storage stability of lenacil residues has been only proven for 254 days. Storage stability data are required to support trials in which samples were stored for more than 254 days. | |

**section 4: Fate and behaviour**

**34. . Fate and behaviour**

| 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 |
|---|---|---|---|
| (0) | General for Fate | EFSA: In the studies by Berg the used soils called Hillsdale and Sassafras are really similar, might could not be handled as two different soil types in the fate assessment. RMS is asked to check the organic carbon content of these soils (in the adsorption/desorption study much lower OC content is reported than values reported in the degradation studies. This inconsistency may come from that somewhere OC%, somewhere else OM% is reported, but it could lead incorrect Kfoc calculation). Moreover the MWHC values of these soils seem to be unrealistically low. Could RMS please clarify whether these soils used in different fate studies come from the same source and give it's view on the point raised in this comment? Moreover please clarify the organic carbon content of these soils and make re-calculations where necessary. | |

**section 4: Fate and behaviour**

| 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, Route and rate of degradation<br>Page 8-3 | EFSA: RMS pls clarify how was DT50 value calculated for metabolite IN-KE121 from the Theis study as the identity of this metabolite is not seem to be confirmed. The text says that metabolites M14.0 and M15.0 were cyclohexanone derivatives - similar to IN-KE121, but it do not say that any metabolite is identical with IN-KE121 (in Appendix 2 of chapter B.8 M15.0 seems to be identical with IN-KE121, but this is not in line with the text or the figures B.8.1-1 and B.8.4.4-1). If neither M14.0, nor M15.0 is identical with metabolite IN-KE121 than $DT_{50}$ of 2.7 d should not be used in the RA, but the leaching potential of M15.0 should be addressed as this metabolites reached > 5% AR at two consecutive sampling time. | See also EFSA comment (8). |

**section 4: Fate and behaviour**

| 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. 3, B.8.1, Route and rate of degradation<br>Study by Berg, 1994a | EFSA: RMS please clarify how long were the soils stored before using them in the study and describe the storage conditions. Please clarify whether the microbiological viability was determined before/during/after the experiments and please give scientifically sound explanation whether the study should be used in the RA or not. Alternatively $DT_{50}/DT_{90}$ could be calculated discarding the lag-phases.<br>Please check whether really OC% is reported or the values refer to OM%. Moreover please confirm whether the values indicated in the Table B.8.1.2.1-1 are referring to the MWHC and not to the actual water content (e.g. at pF 2.5) as at least the value of 12.1% for Sassafras soil seems to be too low. | |

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| 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.8.1, Route and rate of degradation<br>Page 8-7, Table B.8.1.2.1-2 | EFSA: The category „Other polars' seems to contain 1 to 3 peaks. Please indicate the amount of this/these products individually in terms of %AR, as many of the values in this column are >5%. If the individual amount of any of these compounds reaches > 5% AR at two consecutive time point, GW assessment may become necessary.<br>Met.B is increasing at the end of the study therefore GW assessment may be necessary for this compound.<br>Even if that this study is suffering from some shortcomings the exclusion of these metabolites from the residue definition might not been justified. RMS pls. argue why these compounds were not further assessed. | |
| (4) | Vol. 3, B.8.1, Route and rate of degradation<br>Study by Girkin, R., 2003<br>Page 8-8 | EFSA: In the description of the experimental design 40% of MWHC as moisture content is mentioned, but it is not consistent with the values indicated in the Table B.8.1.2.1-3 (16.19 17.17 8.92 21.60 14.81 are not the 40% of 55.01 54.44 37.90 77.46 39.46, respectively). Could RMS please clarify what was the actual water content used for each soils and what superscript a and b in this Table meant? | |

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| 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.8.1, Route and rate of degradation<br>Study by Girkin, R., 2003<br>Tables B.8.1.2.1-4 to B.8.1.2.1-8 | EFSA: RMS please clarify whether the soil samples before the last sampling were taken at day 91 or 88 (DAA) and which was used for the kinetic calculations.<br>RMS please clarify why Polar B was not further addressed as this degradation product appeared at a level >10% AR (also „Polars' in the test at 10°C) and/or >5% at two times. | |
| (6) | Vol. 3, B.8.1, Route and rate of degradation<br>Study by Berg, 1994b | EFSA: RMS pls give details on the results of the analysis of the aliquots extracted from the soils. Please clarify whether was or not any metabolite found in these experiments and which values were used for DT50/DT90 calculations for the metabolite IN-FK313.<br>Moreover pls clarify the same questions as asked for study by Berg, 1994a (storage etc.). | See EFSA comment (2) |
| (7) | Vol. 3, B.8.1, Route and rate of degradation<br>Table B.8.1.2.1-11 & LoEP | EFSA: Some $DT_{90}$ values slightly differ in the LoEP compared with the table in the DAR. | |
| (8) | Vol. 3, B.8.1, Route and rate of degradation<br>Page 8-17, Table B.8.1.2.1-13 | EFSA: As no metabolites IN-KE121 was observed/identified in study by Theis no degradation rate and kinetic fraction could be derived. RMS pls. clarify how these values were derive. | See also EFSA comment (1). |

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| 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, B.8.1, Route and rate of degradation<br>Page 8-17 to 8-18<br>Derivation of $DT_{50}$ soil used for the PEC calculations, Metabolites | EFSA: RMS please clarify the statistical and visual assessment of the fit of the parent compounds and metabolites of the kinetic analysis for each experiment, where the formation fractions and degradation rates of the metabolites were calculated. Please confirm whether both metabolites were associated with the parent directly.<br>RMS please clarify whether the arithmetic mean of the formation fractions were used in the PEC calculations. | |
| (10) | Vol. 3, B.8.1, Route and rate of degradation<br>Tables B.8.1.2.1-15 and B.8.1.2.1-16 & LoEP | EFSA: RMS please clarify why the $DT_{50}$ values from the Whimle soils were leave out from the tables and did not used for the RA. However to incorporate these results into the RA might lead to „better case' situation. | |
| (11) | Vol. 3, B.8.1, Route and rate of degradation<br>Page 8-19 | EFSA: RMS pls include/mention Metabolite IN-KE121 in the Figure (B.8.1-1). | |

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| 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, B.8.1.3<br>Field studies<br>Pollmann, B., 2003 | EFSA: In the calculation of dissipation rates for the German trials the half of the LOQ were used, however the half of the LOD should be used in the case when the measured value is below the LOD and the second value below the LOD should not been used. Where a value is below the LOQ, but above the LOD the actual vale should be used, which may be true for these cases. RMS pls. clarify what was the LOD in this study and what were the actual measured residue values. The repetition of the fitting and the re-calculation of $DT_{50}/DT_{90}$ values as recommended by FOCUS Kinetic guideline might be necessary if the results from this study are used in the RA. | |
| (13) | Vol. 3, B.8.2.1, Adsorption, desorption and mobility<br>Berg, D. S., 1996c | EFSA: The soils Hillsdale and Sassafras used in this study are really similar based on the reported parameters. Moreover the pH range of the applied soils is narrow. | See also EFSA comment (16). |
| (14) | Vol. 3, B.8.2.1, Adsorption, desorption and mobility<br>Kane, T., 2004 | EFSA: The soil Elmton has a $CaCO_3$ content of 263.1 g/kg reported. Is this correct? | |

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| 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 |
|---|---|---|---|
| (15) | Vol. 3, B.8.4.4<br>Water/sediment study | EFSA: Please clarify when the experimental samplings were taken as this information is not perfectly clear from the text especially when compared with the heading of the tables (B.8.4.4-2 and B.8.4.4-3) and check whether the correct time points were used for the kinetic calculations. Moreover please clarify what is the difference between Recovery (mean) and Total recovery (mean) in the Tables B.8.4.4-2 and B.8.4.4-3. | |
| (16) | Vol. 3, B.8.6.1<br>PEC groundwater and surface water<br>Table B.8.6.1 | EFSA: $DT_{50}$ values used for PEC GW and SW calculations are neither the arithmetic mean nor the geomean (or median) values based on the considered dataset by the RMS (and all of them are shorter than the geomean).<br>As the pH range of the soils used for the determination of adsorption/desorption for the metabolite IN-KF313 was narrow and two soils from the three were really similar to each other the worst case Kfoc value of 79 and 1/n of 1 should arguably be used for the calculations (or additional data would be needed).<br>The same MW was used for the two metabolites, which might be correct, but should be confirmed/re-checked.<br>As the present calculation may underestimate the risk for GW and SW (at least for GW in the case of the metabolite IN-KF313) re-calculation might become necessary. | See EFSA comment 0 and EFSA comment 13. |

* 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.

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| 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 |
|---|---|---|---|
| (17) | Vol. 3, B.8.6.1<br>PEC groundwater and surface water<br>Table B.8.6.1 | EFSA: RMS pls clarify whether or not the calculated crop washoff factor was used only for SW calculations and please confirm that the crop half-life was not changed for the modelling. The change on crop washoff factor should be indicated in the relevant part of the LoEP. | |
| (18) | Vol. 3, B.8.10 References relied on | EFSA: If the RMS belives that the studies by Berg (Berg, D. S. 1994a and Berg, D. S. 1994b) are not relied on they should be removed from the list of References relied on. | |

**section 5: Ecotoxicology**

**35. . Ecotoxicology**

| 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.9.1.2, Avian dietary toxicity | EFSA: The RMS states that $LC_{50}$ was converted to daily dose based on mean bw of 5.7 g/bird but the mean weight at the start was 13.0-14.0 g. Could you please clarify? It would be more transparent to have raw data (i.e tables with the body weight and food consumption during the test) | |
| (2) | Vol. 3, B.9.1.3, Avian reproduction toxicity | EFSA: the raw data should be reported for causes of transparency (i.e tables with the body weight and food consumption during the test). | |
| (3) | Vol. 3, B.9.2.8, effects on algae, *Navicula pelliculosa* study | EFSA: in the "Flatman D., 2003b" study only the measured concentrations are reported. It is not clear which nominal concentrations were applied as well as the difference between the nominal and the measured concentrations. | |
| (4) | Vol. 3, B.9.2.8, effects on algae, *Selenastrum capricornutum* study | EFSA: in the "Flatman D., 2003c" study only the measured concentrations are reported. It is not clear which nominal concentrations were applied as well as the difference between the nominal and the measured concentrations. | |
| (5) | Vol. 3, B.9.2.10, effects on aquatic plants, *Lemna* study | EFSA: in the "Flatman D., 2003d" study only the measured concentrations are reported. It is not clear which nominal concentrations were applied as well as the difference between the nominal and the measured concentrations. | |

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**section 5: Ecotoxicology**

| 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.9.2.11, acute toxicity of the preparation, *Selenastrum capricornutum* study | EFSA: Since the study was not acceptable, it cannot be used in risk assessment. It should be deleted from the LoE and from the list of studies relied on. A new valid study could be useful to address potential highest sensitivity of algae to the formulation with respect to the active ingredient.<br>According to the available data, algae and aquatic plants drive the risk assessment. The submitted higher tier studies address particularly the effects on aquatic plants. Therefore if algae are more sensitive the available data could be not sufficient to address the risk to algae. | |
| (7) | Vol. 3, B.9.2.12, aquatic organisms, microcosm and mesocosm study (Taylor S.A., 2004) | EFSA: The RMS states that the "Taylor S.A., 2004" study is not acceptable. Was the study not accepted because the concentrations were not determined analytically?<br>This study confirms the highest sensitivity of *Elodea canadensis* observed in the outdoor microcosm study (Jenkins C.A., 2005). Therefore, the study could be useful to cover uncertainties observed in such outdoor microcosm study (see related EFSA comment). Could the RMS please re-evaluate the acceptability of the study? | |

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| 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 |
|---|---|---|---|
| (8) | Vol. 3, B.9.2.12, aquatic organisms, microcosm and mesocosm study (Jenkins C.A., 2005) | EFSA: several uncertainties can be observed in the outdoor microcosm study (Jenkins C.A., 2005).<br>From the summary reported in DAR, it is not clear where the study was conducted. Could the study be considered acceptable for both the northern and southern EU intended uses? (The sunlight is a limiting factor for macrophyte growth).<br>The results of the statistical analysis of the different parameters are not reported (i.e. PRC).<br>Could the influence on growth rate/abundance of other limiting factors (for instance $O_2$, Nitrate, sulphate, phosphates) be excluded? It would be better to have the results of the additional water chemistry analysis.<br>The study was performed with a single application. Could a single application be considered to cover the intended uses (1 to 4 applications, 7 to 14 days interval)?<br>How could be explained the presence in the study of the species reported under the paragraph "*other macrophytes species*" at page 9-31? Could the observations related to these species be considered reliable? One of the most sensitive species (*Charophyita*) belongs to this group, thus it would be better to have more details.<br><br>In general, it would be appreciated to have a more detailed summary with all the necessary raw data | |

**section 5: Ecotoxicology**

| 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, B.9.4.1, Acute toxicity to bees | EFSA: RMS states that the acute oral toxicity study of Hoxter K.A. *et al* 1994a, is not acceptable because the endpoint is not expressed in µg a.s./bee. Anyhow, it would be better to report the study result (i.e. the resulted endpoint). | |
| (10) | Vol. 3, B.9.9 Effects on other non –target organisms (flora and fauna) | EFSA: it is surprising that lenacil does not cause adverse effects on non-target plants, as though it is a non-selective herbicide which inhibits the chlorophyll synthesis. How can this be explained? | |