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Comments on the Draft Assessment Report on folpet (EAS)

RMS IT

End of commenting period: 17.09.2004 (MS, NOT)

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26.07.2004 05.08.2004	France	01 folpet comments FR 2004-08-05 fate.doc 01 folpet comments FR 2004-07-26 ecotox.doc
16.09.2004	Notifier	02 folpet comments NOT 2004-09-16.doc
16.09.2004	The Netherlands	03 folpet comments NL 2004-09-16.doc
17.09.2004	United Kingdom	04 folpet comments UK 2004-09-17.doc
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11.10.2004	Slovenia	10 folpet comments SL 2004-10-11.doc

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

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.8.1.1, Aerobic and anaerobic studies	FR: in Table B.8.1.1.2, bound residues seem to have been underestimated (for example on day 14 fulvic acid fraction =14.6 % in text and bound residues = 9.2 % in table). Could this point be clarified.	
(2)	Vol. 3, B.8.1.1, Aerobic and anaerobic studies	FR: from Table B.8.1.1.2, the apparent DT50 for phthalimide is 7.3 d using linear 1^{st} order for the 5-30 d period (R^2 0.81) at 25° C or 10.6 d at 20° C (1^{st} order should be preferred instead of square root 1^{st} order).	
(3)	Vol. 3, B.8.1.1, Aerobic and anaerobic studies	FR: in table B.8.1.1.9 it is not clear why fulvic acid and humic acid fractions were excluded from bound residues. Could this point be clarified.	
(4)	Vol. 3, B.8.1.1, Aerobic and anaerobic studies	FR: the second aerobic/anaerobic study should not be used (significant deviation from guideline). The first study suggests that anaerobic degradation could be similar to aerobic degradation but would occur at slower rate.	
(5)	Vol. 3, B.8.2.1, Adsorption and desorption	FR: Koc for phthalamic acid and phthalic acid has been estimated by means of the EWIWIN program but this is not described in the monograph. This point should be completed.	
(6)	Vol. 3, B.8.6, Groundwater	FR: for phthalimide, the lower Kdoc (56) was used for PECgw calculation. However Kfoc was available and was < Kdoc. Could this choice be explained. For phthalamic acid and phthalic acid it is stated that PECgw are not expected to exceed 0.001 µg/L but the input parameters have not been specified so it is not possible to conclude (even if low risk is expected with regard to fast degradation). This point should be completed.	
(7)	Vol. 3, B.8.6, Surface water	FR: PECsw should be calculated for the metabolites.	

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

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(8)	Vol. 1, appendix 3, list of end points	FR: because 2 label positions were used, mineralization and non-extractable residues should be reported for each moiety.	
(9)	Vol. 1, appendix 3, list of end points	FR: from table B.8.1.1.6, the metabolites phthalamic acid and phthalic acid can exceed 10 % in aerobic soils. This should be reported in the end points.	
(10)	Vol. 1, appendix 3, list of end points	FR: the rate of degradation of the metabolites phthalamic acid and phthalic acid should be reported in the end points.	
(11)	Vol. 1, appendix 3, list of end points	FR: it is not clear why the Freundlich adsorption parameters for phthalimide have not been reported in the end points.	
(12)	Vol. 1, appendix 3, list of end points	FR: results from the aged residues leaching (Heintz, 2001) should be summarized in the end points.	
(13)	Vol. 1, appendix 3, list of end points	FR: the DT50 value used for PEC soil calculation should be specified in the end points.	
(14)	Vol. 1, appendix 3, list of end points	FR: the hydrolysis products should be reported in the end points.	
(15)	Vol. 1, appendix 3, list of end points	FR distribution/amounts of folpet and its metabolites in water and sediment should be reported in the end points as well as DT50 values.	
(16)	Vol. 1, appendix 3, list of end points	FR: values of the input parameters (DT50 and Koc) used for PECgw calculation should be reported in the end points.	

5. Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	Vol. 3, Annex B, point B.9.1.3. risk to birds.	FR: folpet is intended to be used for a period ranging from 2 weeks to up to 10 weeks in some crops (e.g. vineyards). It is not sure that the risk arising from repeated exposure over a 2-month and a half period is addressed by the proposed calculations.	
(2)	Vol. 3, Annex B, point B. 9.2.5., risk to aquatic organisms	FR: it is proposed in the DAR to re-assess risks based on a probabilistic approach. We are not convinced that a safety factor of 10 is sufficient as the assessment remains based on acute effects. Moreover it is not clear how this safety factor was introduced into calculations. In addition, it is not so sure that under field conditions a chronic exposure would not occur because application occur each week during up to 2 months and a half. Finally, DT50 of metabolites should be reminded to support the hypothesis of a lower PEC than the PEC for the parent. It should be demonstrated that their DT50 is so low that multi-application is not relevant to calculate PECsw for metabolites.	

section 5 - Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(3)	Vol. 3, Annex B, point B.9.3.2, risk assessment to mammals.	FR: folpet is intended to be used for a period ranging from 2 weeks to up to 10 weeks in some crops (e.g. vineyards). It is not sure that the risk arising from repeated exposure over a 2-month and a half period is addressed by the proposed calculations.	
(4)	Vol 3, Annex B, point B.9.4.2.1.2.toxicity of formulated products to bees	FR: the summary of the study references Nengel, 1996c is exactly similar to the summary of the study referenced Nengel, 1996a. is this the same study?	
(5)	Vol 3, Annex B, point B.9.6.3., risk to earthworms	FR: the use of twaPEC for long term risk assessment is not justified since dissipation of the a.s. within time was already considered in the reproduction test. Moreover, this is not conservative when considering repeated uses of folpet. If PEC had to be time-weighted, it should rather be done over a 7 days interval (interval between applications) which would be more representative of the expected exposure of soil organisms. Moreover, it is proposed that metabolites are covered by the risk assessment with the parent, but this is not true anymore if PEC are time-weighted.	

section 2 - Mammalian toxicology (B.6)

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

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, 4.5, and Vol 3, B.5.2.1, methods of analysis in plants, plant products	The DAR volume 1 concludes the following: Analytical methods are available for all of these crop groups, but confirmatory assays have been provided only for wheat. Confirmatory assays for all crops other than wheat are required. This deficiency identified by the RMS has been addressed (see Column 3) and in conclusion, no additional data are considered necessary.	Confirmatory procedures It is considered that residues may be confirmed using the many other chromatographic conditions presented for folpet residue determination (crops, soil, water, air). These methods are based on capillary GC with electron capture detection using a range of stationary phases of varying polarity and reverse-phase HPLC with either ultraviolet or diode array detection. The various conditions will be sufficient for use in confirmation of folpet residues. The guidance document SANCO/825/00 states that acceptable confirmatory techniques may be based on differences in the chromatographic principle (HPLC, GC), alternative detection, and different stationary and/or mobile phases. Therefore, it is considered unnecessary to conduct further work on confirmation when there are numerous existing chromatographic conditions available. Summaries of all the analytical methods, the validation data, a summary of the various chromatographic methods available for determination of folpet and the response to the data requirements/deficiencies are presented in the following position paper: **"Folpet. Position Paper on Residue Analytical Methods (May 2004)".** Will be included in the addendum to be submitted to the RMS.

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

section 2 - Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(2)	Vol. 1, 4.5, and Vol 3, B.5.2.2, methods of analysis in animal tissues and milk	The DAR volume 1 concludes that the method can be acceptable in principle, but requires independent laboratory validation and a confirmatory assay. It is considered unnecessary to conduct further work or confirmation when there are numerous existing chromatographic conditions available and an analytical method for monitoring purposes is not required due to the lack of residues of folpet in edible animal tissues.	It is considered that the analytical method described by Mende under Annex Point IIA, 4.2.1/06 has been adequately validated in all respects except that an independent laboratory validation has not been conducted. The comments above regarding confirmation for crop residue methods also apply to animal tissue methods - it is considered that residues may be confirmed using the many other chromatographic conditions presented for folpet residue determination (crops, soil, water, air). These methods are based on capillary GC with electron capture detection using a range of stationary phases of varying polarity and reverse-phase HPLC with either ultraviolet or diode array detection. The various conditions will be sufficient for use in confirmation of folpet residues. The guidance document SANCO/825/00 states that acceptable confirmatory techniques may be based on differences in the chromatographic principle (HPLC, GC), alternative detection, and different stationary and/or mobile phases. Therefore, it is considered unnecessary to conduct further work on confirmation when there are numerous existing chromatographic conditions available. In any case, due to the absence of independent laboratory validation, it is considered appropriate to retract the original claim in the dossier that the method is suitable for monitoring purposes. However, further validation work is not required for the following reason.

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			The metabolism studies in goat demonstrated that residues of folpet in edible animal tissues following administration of a worst-case dietary concentration were below the limit of quantification. Therefore, feeding studies in ruminants are not required. Metabolism and feeding studies in poultry are not required as the dietary concentration of folpet is less than 0.1 mg/kg total diet as received. Consequently, MRLs for animal tissues, milk and eggs are not applicable. Therefore, an analytical method for monitoring purposes is not required under these circumstances (as defined by Commission Directive 96/46/EC) and the validity of the methods presented need not be evaluated. The method presented for determination of folpet in animal tissues, eggs and milk should be considered as supporting information for the methods dossier and any deficiencies in their validation are irrelevant. Summaries of all the analytical methods, the validation data, a summary of the various chromatographic methods available for determination of folpet and the response to the data requirements/deficiencies are presented in the following position paper: **"Folpet. Position Paper on Residue Analytical Methods (May 2004)".** Will be included in the addendum to be submitted to the RMS.
(3)	Vol. 1, 4.5, and Vol 3, B.5.4, methods of analysis in body fluids and tissues	The DAR volume 1 concludes that a validated method is required. This data requirement is not applicable to folpet.	Commission Directive 96/46/EC and the EU guidance document SANCO/825/00 both state that methods for the determination of residues in body fluids and tissues are only required for those active substances that are classified as toxic or highly toxic. Folpet is not classified as toxic or highly toxic and, therefore, analytical methods for body fluids and tissues are not required.

2. Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	Vol. 1, 4.6, and Vol 3, B.6.6 reproductive toxicity	The DAR volume 1 concludes that new teratogenic studies in rat and rabbit are required with histopathological examination of the gastro-intestinal tract of the mothers. Based on several factors (see column 3), we believe no useful information would be gained from further reproductive or developmental toxicity studies conducted with folpet.	Reproductive toxicity studies The NOEL for effects on pup body weight for folpet in reproductive toxicity studies is revised from 12.5 mg/kg bw/day to 40 mg/kg bw/day, based on a weight-of-the-evidence evaluation of the two studies. This dose level is equivalent to the parental NOEL, demonstrating a lack of unique susceptibility of the young to folpet toxicity. Using 12.5 mg/kg bw/day as the basis for the folpet AOEL as currently recommended provides a very conservative additional margin of safety for risk extrapolation. Developmental toxicity studies We concur with the RMS reviewer that the axial abnormalities observed at maternally toxic dose levels in several folpet developmental toxicity studies may be related to the maternotoxic effect elicited by folpet on the gastrointestinal tract. In addition to the noted irritant action of folpet on the gastrointestinal mucosae, high bolus gavage doses of folpet are likely to adversely affect the intestinal flora, leading to nutrient malabsorption or deficiencies. The developmental NOAELs for folpet are 150 mg/kg bw/day and 40 mg/kg bw/day, for the rat and rabbit, respectively. There is no evidence of unique susceptibility of the foetus to folpet, and a weight-of-the-evidence evaluation does not support a conclusion that folpet is teratogenic. Further, distribution of folpet to the foetus is considered unlikely because of the very short half-life of folpet in aqueous media, and the primary

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			metabolite phthalimide produced no malformations in a supplementary teratogenicity evaluation in rabbits. Conclusion The existing database provides adequate information regarding the reproductive and developmental toxicity of folpet to permit informed and conservative risk assessment. There is no evidence that there is any unique developmental susceptibility of the developing young to folpet. Further reproductive or developmental toxicity testing of folpet should not be required Response to the Requirement for Further Reproductive or Developmental Toxicity Studies of Folpet The existing database provides adequate information regarding the reproductive and developmental toxicity of folpet to permit informed and conservative risk assessment. For reproductive toxicity evaluation, we concur with the RMS reviewer that in cases where the studies are not congruent with existing guidelines, the absence of any evidence of reproductive toxicity in a study producing overt toxicity to the parental animals suggests no additional useful information would be obtained from further studies. For developmental toxicity evaluation, we respectfully disagree with the reviewer that additional useful information would be obtained through replication of the rat and rabbit developmental toxicity studies, and that animals and resource expenditure in such an effort is therefore not justifiable. The basis for our conclusion is that: • Existing studies comply with Guidelines in effect at the time the studies were performed, and provide information on the most

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			critical elements in current Testing Guidelines. • NOELs are available for all endpoints of concern, • Folpet does not show unique evidence of developmental susceptibility, and a weight-of-the evidence evaluation does not support a concern for teratogenicity. The one remaining question is that the postulated mechanism for maternotoxicity resulting in the axial respecifications observed in several developmental studies of folpet at maternally toxic dose levels has not been clearly demonstrated in the existing data. If this mechanism were confined to nutritional deficiencies resulting from gastrointestinal irritation, it could possibly be demonstrated through histopathological evaluation of the maternal gastrointestinal tract. However, it seems likely that the bacteriostatic action of folpet when administered in high gavage doses also plays a significant role in subsequent maternal nutrient deficiencies, contributing to the axial respecifications observed in some studies of captan. Such a mechanism would not be possible to demonstrate in a conventional developmental toxicity study, and it is difficult to conceive of a study design to adequately test this mechanism. Folpet is used commercially as a bacteriostat in cosmetic formulations, and evidence of bacteriostatic action of captan (which is a closely structurally related chemical) is available in the published literature. Based on these factors, we believe no useful information would be gained from further developmental toxicity studies of folpet. Full and detailed comments on all aspects on the reproductive toxicity and teratogenicity of folpet will be presented in a position paper to be included in the addendum to be submitted to the RMS.

section 2 - Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(2)	Vol. 1, 2.3.3	An ARfD of 0.1 mg/kg bw is proposed. We propose that, based on an evaluation of the toxicology database for folpet, an ARfD for folpet is not needed.	An ARfD is not required for folpet for the following reasons: 1) There is minimal irritation seen in the gastrointestinal tract after one day exposures to folpet at doses above 500 mg/kg. 2) There are minimal effects at doses above 500 mg/kg in a development study. 3) Gastrointestinal irritation following repeated folpet oral exposure is rapidly reversed upon cessation of treatment. 4) Folpet is not present in the systemic circulation and is not a systemic toxin. 5) Folpet will not induce adverse effects when residues are ingested continuously, even at the theoretical maximum residue values. 6) Folpet's oral toxicity is greater than 5 g/kg. Full and detailed comments on all aspects of the ARfD for folpet are presented in a position paper: **"Gordon, E (2004). Folpet. A summary basis for why an acute reference dose (aRfD) is not needed. Submitted to the JMPR for the 2004 toxicological evaluation of folpet"**. This position paper is supported by a new previously unsubmitted acute intestinal irritation study, namely **"Moore, G.E. and Creasey, D. (2004). Intestinal irritation in CD-1 mice after a 24-hour exposure to folpet. [redacted] unpublished report number 13763 (Company file: R-16283)"**

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			This study concludes that folpet administered by oral gavage at 900 mg/kg/bw or in the diet for 24 hours at 5000 ppm (as well as 500 ppm, 200 ppm, and 50 ppm) caused only minimal ("borderline") irritation of the proximal duodenum. The initial finding of apparent irritation in the first study was shown to be due to artefacts upon thorough (eight step serial section) examination of the expanded second study. It was concluded that folpet was borderline for producing irritancy at 5000 ppm. The position paper and the new study will be included in the addendum to be submitted to the RMS.
(3)	Vol. 3, B.6.1.1	A study to measure the half-life of folpet in whole blood is included in the DAR (see page 13 of Volume 3). A new study is available which reports the half-life of thiophosgene (a folpet degradate) in human blood.	A method to measure the presence of thiophosgene in human blood was developed. Blood was fortified with thiophosgene, quenched with an acidic acetone solution and the remaining thiophosgene was derivatized to the cyclic compound (R)-2-thioxo-4-thiazolidinecarboxylic acid using L-cysteine and analyzed by HPLC-UV. Pre-quenched blood fortified with 10, 30 and 100 µg/mL thiophosgene resulted in an average recovery of 42% ± 8.6%. The method was employed to measure the half-life of an exaggerated concentration of thiophosgene (100 µg/mL) in human blood. Thiophosgene was added to 10 human blood samples (at 37˚C) and allowed to react for times ranging from 1.9 seconds to 31.1 seconds. The reactions were then arrested and the remaining thiophosgene was determined. The thiophosgene % recovered data was normalized to account for a threshold level of about 1% found in samples reacted for at least 7 seconds believed to be attributed to saturation of the relevant blood nucleophiles by the exaggerated rate of thiophosgene employed. An exponential equation (of the form $y = a + b*\exp^{(-k*x)}$) was used to fit the

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			normalized % thiophosgene recovered vs. reaction time data with a correlation coefficient of > 0.99 when the data point of 100% recovery at time zero is assumed. The half-life of thiophosgene in human blood was found to be 0.6 seconds. This study demonstrates why neither folpet (with the DT_{50} of 4.9 sec. in human blood) nor thiophosgene are likely to reach sensitive target distant to the mucosal surface of the gastrointestinal tract and as part of the mechanism data it further supports the folpet mode of action. The new study is listed below: **"Arndt, T and Dohn, D. (2004). Measurement of the Half-Life of Thiophosgene in Human Blood. PTRL West unpublished report number 1146W-1"** This new study and our evaluation of this study (in Tier 2 format) will be included in the addendum to be submitted to the RMS.
(4)	Vol. 1, 2.3.3	An AOEL of 0.125 mg/kg bw is proposed in the DAR based on a NOEL of 12.5 mg/kg bw/day from the 2-generation study. However, taking the two reproductive toxicity studies together, the NOEL for the critical developmental effect is 800 ppm, equivalent to approximately 40 mg/kg bw/day. The AOEL should be based on the NOEL of 40 mg/kg bw/day, which with a safety factor of 100, gives an AOEL of 0.4 mg/kg bw/day.	Dietary administration of folpet at a concentration of 5,000 ppm for two generations (Rubin 1986) resulted in reduced body weight and food consumption of the parental animals and reduced body weights of the offspring from Day 7 *post-partum* of the F_0 generation and on Day 21 of the F_1 generation. At 1,500 ppm, slight but statistically significant reductions in body weight were seen in the parental animals and also in the offspring from Day 21 of the F_0 generation. There were no effects on the pregnancy rates, fertility indices, gestation periods and litter sizes at any of the dose levels. Findings at histopathological examination showed effects on the target organs at 5,000 and 1,500 ppm, including hyperkeratosis of the non-glandular stomach in both generations with

section 2 - Mammalian toxicology (B.6)

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			occasional incidences of squamous epithelial hyperplasia in high dose F_0 males and one incidence of focal inflammatory ulceration in the high dose F_1 males, increased incidences of the foci of renal basophilic tubules in high dose males of both generations, and hyperkeratosis of the oesophagus in intermediate and high dose F_1 females. This increased incidence of hyperkeratosis of the oesophagus in the F_1 females, when there was no occurrence in the F_0 generation, may be explained either by the younger age of these animals at the start of treatment possibly increasing susceptibility to this lesion at this site, or by the longer duration of exposure to folpet in the F1 generation increasing the opportunity for the lesion to develop. (The lesion was seen only on examination of adult animals, and not on examination of pups.) The hyperkeratosis reflects the direct irritant agent of the compound, and whether oesophageal or in the non-glandular stomach has origin in a similar tissue type by the same mechanism. It shpuld be noted that direct exposure to the F1 animals starts prior to weaning, and by the time of weaning the amount of test material consumed is, on a bodyweight basis, 2-3x the amount consumed by an adult rat. Thus no quantitative difference in susceptibility is demonstrated by this F1 finding, but rather the effects of the increased feed consumption and lower body weights during the rapid peri-weaning growth period. In a second two generation study (Richter 1985), with each generation producing two litters, administration of 3,600 ppm in the diet resulted in lower body weights and food consumption in the F_0 males and in the F_1 males and females, although the F_1 female body weight change was comparable to the controls. Mean pup weights in all litters were reduced by Day 21 in the F_0 generation and on Days 14 and 21 in the F_1 generation. There were no effects at 800 or 200 ppm administration.

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			There were no effects on the mating performance, pregnancy rates, fertility indices, gestation periods and litter sizes at any of the dose levels in the F_0 generation. There was a slight decrease in the pregnancy rate and fertility index for both matings with the F_1 animals in the intermediate and/or high dose groups but was not significant; other indices and litter sizes for the F_1 generation were without effect. There were no treatment–related findings at the macroscopic and microscopic examinations (it should be noted that stomach tissues were not examined microscopically in this study). The multigeneration studies performed with folpet do not include assessment of all of the latest guideline reproductive parameters (vaginal smears were taken, but spermiology and hormonal assessments were not performed). There is no need to perform further investigations, as the present studies showed a definite adult maximum tolerated dose (MTD), with no adverse effects on reproduction. There were no adverse histopathological findings in testes of rodents or dogs in longer-term studies, and no indication of a dominant-lethal effect. There is no need to investigate specific possible effects of folpet on hormonal systems, because the half-life of Folpet in blood is so short (4.9 seconds, see Point IIA 5.1/05), any active substance that may be systemically available would degrade rapidly. The multi-generation studies of folpet were conducted using the same rat strain and similar conditions of exposure. Thus the data may be combined in a weight-of-the-evidence assessment to derive the NOEL for the critical reproductive or developmental effect. Neither study demonstrated significant reproductive toxicity potential for folpet, up to the highest dose tested (5,000 ppm in the Rubin study). Adult toxicity

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			included decreased weight gain and hyperkeratosis of the oesophagus and non-glandular stomach at 1,500 ppm and higher in the Rubin study, and decreased weight gain in the Richter study at 3,600 ppm. (Stomachs were not evaluated microscpically in the Richter study.) The NOEL for the body weight effect in the Richter study was 800 ppm. This was also the NOEL for hyperkeratosis of the stomach at one year in the Cox 1985 chronic toxicity oncogenicity study which was conducted with SD rats. Thus an adult NOEL can with confidence be set at 800 ppm, using the data from both reproductive toxicity studies, supplemented by the one-year data form the chronic toxicity study using the same rat strain. Toxicity to the pups was limited to decreased body weight gain in both studies. This was evident in the Rubin study at dose of 1,500 ppm ; the weight gain decreases were slight but statistically significant at PND 21 of the F0 generation. In the Richter study, this finding was made at 3,600 ppm, but not at 800 ppm. Taking the two reproductive toxicity studies together, the NOEL for this critical developmental effect is 800 ppm, which is equivalent to approximately **40 mg/kg bw/day**. **[Note this effect was used as the driving effect/study for the AOEL; however, in drafting the original monograph, the two reproductive studies were not analyzed together, leading to the erroneous conclusion that the NOEL was 12.5 mg/kg bw/day.]** Full and detailed comments on all aspects on the reproductive toxicity and teratogenicity of folpet will be presented in a position paper to be included in the addendum to be submitted to the RMS.

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section 3 - Residues (B.7)

3. Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	Vol. 1, 4.7, and Vol 3, B.7.7.1 effects of processing on the nature of the residue	The DAR Volume 1 concludes that a hydrolysis study in representative hydrolytic conditions is required. It is concluded that sufficient data already exist to predict the effect of processing hydrolysis on the nature of the residue and therefore new studies are not required.	Hydrolysis studies with folpet have already been conducted and are considered to be adequate to evaluate the effects of processing. Under acid conditions (pH5) [carbonyl-^{14}C] folpet degraded rapidly to phthalimide with phthalamic acid and phthalic acid also observed at lower levels. Under neutral conditions (pH7) the same metabolites were observed, but with the amounts formed shifted in favour of phthalic acid. Phthalimide is hydrolysed, via phthalamic acid, to phthalic acid. Phthalic acid is the stable end point of [carbonyl-^{14}C] folpet hydrolysis under acid and neutral conditions. In the study with [trichloromethyl-^{14}C] folpet, the primary metabolite formed under acid and neutral conditions (pH5 and pH7) was carbon dioxide. The pH conditions of the proposed simulated processing study (pH, 4, 5 and 6) would expose folpet residues to the same conditions as those described in the above tests. Therefore the stable hydrolytic end points (phthalic acid and carbon dioxide) are expected to be the same. The only effect of increased temperature in a simulated processing study will be to drive the hydrolytic reaction to its conclusion at a faster rate. At pH4 and 100°C phthalimide degrades with a half-life of 5.5 hours, considerably longer than the incubation time required in the proposed tests. Therefore, studies under simulated processing conditions would only provide additional data on the rate of formation of the known degradation products and would not alter the route of degradation already established.

section 3 - Residues (B.7)

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			The metabolites phthalimide and phthalic acid are not considered to be of toxicological concern because they were found in both plants and animals and do not form part of the definition of the residue in crops. Potentially toxic metabolites would not be formed during a simulated processing study and so a new study is not considered necessary. The requirement for a new study and the response to the data requirement is fully addressed in the following position paper: **"Folpet. Position Paper on Effects on the Nature of the Residue (2004)".** Will be included in the addendum to be submitted to the RMS.
(2)	Vol. 1, 4.7, and Vol 3, B.7.7.2 effects of processing on residue levels	The DAR Volume 1 concludes that new processing studies (1 balance plus 3 follow up studies) in tomato are required. Studies are ongoing.	
(3)	Vol. 1, 4.7, and Vol 3, B.7.6.1 residue trials in tomato	The DAR Volume 1 concludes that two new residue studies in greenhouse tomato are required. A new freezer stability study to validate additional crop residue studies in greenhouse tomato is ongoing.	Some residue trials in greenhouse grown tomatoes submitted in the dossier were rejected by the RMS due to an excessive storage period between sampling and analysis (see page 188 of Volume 3 of the DAR). A new freezer storage stability study is ongoing and will be submitted to validate the rejected trials instead of conducting new trials in greenhouse tomatoes.

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

4. Environmental fate and behaviour (B.8)

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

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5. Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	Vol. 1, 2.6.1, and Vol 3, B.9.1 and B.9.3	In response to a request from the RMS, a revised risk assessment for birds and wild mammals has been conducted, in accordance with the 'Guidance Document on Risk Assessment for Birds and Mammals under Council Directive 91/414/EEC' (SANCO/4145/2000); 25 September 2002. This concludes that overall, there is a low risk to birds and mammals.	The revised risk assessment in accordance with the 'Guidance Document on Risk Assessment for Birds and Mammals under Council Directive 91/414/EEC' (SANCO/4145/2000); 25 September 2002, concludes that overall, there is a low risk of folpet to birds and mammals. The risk assessment is presented in the paper below: **"Norman, S. and Wyness, L. (2003). Folpet: Response to Rapporteur Member State request for a revised avian and mammalian risk assessment in accordance with EU Guidance Document on Risk Assessment for Birds and Mammals (SANCO/4145/2000."** Will be included in the addendum to be submitted to the RMS.
(2)	Vol. 1, 2.6.3, and Vol 3, B.9.5	The DAR Volume 1 concludes that new laboratory studies on arthropods with GAP application rates are required. Additional studies have been undertaken on four species which cover the proposed rates and the ESCORT 2 multiple application factor. Based on the new studies, it is concluded that there is a low risk to non-target arthropods in-field and off-field.	Data have been reviewed by the RMS on toxicity to non-target arthropods. These studies indicated a general low toxicity. The application rates tested in the laboratory and extended laboratory studies do not cover the highest rates notified in the EU review. Hence, additional extended laboratory studies have been undertaken on *Aphidius rhopalosiphi*, *Typhlodromus pyri*, *Coccinella septempunctata* and *Chrysoperla carnea* which cover the proposed rates, and also the ESCORT 2 multiple application factor (MAF). Testing on these four species represents a complete dataset under ESCORT 2. From the proposed uses, the worst case is use on grapevines with a maximum of 10 applications at 1.5 kg a.s./ha. The highest rate in the new studies (5.25 kg a.s/ha, including MAF) was selected to cover the grapevine use. At this rate, there were no significant effects on *T. pyri*, *C. septempunctata* or *C. carnea*. *A. rhopalosiphi* gave 76% mortality at 5.25 kg/ha for fresh residues (i.e.

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section 5 – Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
			greater than ESCORT 2 trigger of 50%). Effects for fresh residues were less than 50% for 3.38 kg a.s./ha (to cover proposed use on tomato). For 14 day aged residues at 5.25 kg/ha, there were no effects on *A. rhopalosiphi*. Hence, the ESCORT 2 criterion for potential for recovery/recolonisation within 1 year is satisfied. Overall, it can be concluded that there is a low risk to non-target arthropods in-field and off-field. The new studies and the updated risk assessment are listed below: **Moll, M., Bützler, R (2004). Effects of Folpan 80 WDG on the parasitoid *Aphidius rhopalosiphi*, extended laboratory study, aged residue test. Unpublished report. IBACON project number 18201003. Date: 13 January 2004. (Company file R-16400).** **Moll, M (2004). Effects of Folpan 80 WDG on the ladybird beetle *Coccinella septempunctata*, extended laboratory study, aged residues test. Unpublished report. IBACON project number 18203013. Date: 13 January 2004. (Company file R-16402).** **Rosenkranz, B. (2004a). Effects of Folpan 80 WDG on the predatory mite *Typhlodromus pyri*, extended laboratory study, aged residues test. Unpublished report. IBACON project number 18202060. Date: 27 January 2004. (Company file R-16401).** **Rosenkranz, B. (2004b). Effects of Folpan 80 WDG on the lacewing *Chrysoperla carnea*, extended laboratory study, aged residues test. Unpublished report. IBACON project number 18204048. Date: 27 January 2004. (Company file R-16398).**

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section 5 – Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
			"Norman, S. (2004). EU Review of folpet: Non-target arthropods: Updated risk assessment incorporating new extended laboratory studies at higher application rates than previously tested." The new studies (and Tier 2 summaries of the new studies) and the new risk assessment paper will be included in the addendum to be submitted to the RMS.

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

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

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

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section 2 - Mammalian toxicology (B.6)

2. Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	Vol.1, List of endpoints, Short-term toxicity, oral.	NL RMS gives a lowest relevant oral NOAEL of 44.5 mg/kg bw/d from a 90d feeding study with rats. Based on the 4 studies with dogs (4 wk, 13 wk and 2x 1y) it is clear that the dog is more sensitive to adverse effects of folpet. Since the NOAEL in the 4 wk study was < 20 mg/kg bw/d and the NOAEL for 1 y studies in dogs is 10 mg/kg bw/d, the most relevant short term NOAEL is 10 mg/kg bw/d.	NOAEL's short term rat and dog 90d rat 44,5 mg/kg bw/d (m), 58,5 mg/kg bw/d (f) (N.B.: in the text in Vol 1. p.20, Vol.3, B.6.53.5 other values are given for the NOAEL, i.e. 67 mg/kg bw/d (m) and 56 mg/kg bw/d (f) 4 wk dog <20 mg/kg bw/d 13 wk dog <790 mg/kg bw/d 1 y dog <325 mg/kg bw/d 1 y dog 10 mg/kg bw/d
(2)	Vol. 1, 2.3.4, Vol. 3, BB.6.10.3, list of end points, Derivation of AOEL	NL Since the dog is clearly more sensitive in short term studies, the AOEL should be based on the NOAEL of 10 mg/kg bw/d in the 1 y dog studies.	

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section 2 - Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(3)	Vol. 3, B.6.12, Dermal absorption List of endpoints	NL Disagree with the value of 1% for dermal absorption based on the information in the DAR. RMS concludes to a dermal absorption of 1%, based on an vitro study with rat and human skin and a publication of in vivo data in rats. The data are entirely based on the amount absorbed through the skin. No data are given for the amount of folpet in the treated skin (dermal depot) and its possible systemic availability. In the in vitro study the amount absorbed through the skin is much higher after 24 h than after 8 h exposure. This could (at least partly) be the result of dermal depot becoming systemically available. Without data on the dermal depot a higher value for dermal absorption should be considered. Since the study was done in a laboratory which always gives data on the dermal depot in its report, a better estimation of dermal absorption should be possible.	

section 3 - Residues (B.7)

3. Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.7.15, Acute exposure	NL : Although an ArfD has been proposed, no acute dietary intake calculations are presented in the monograph. On the basis of the Dutch food consumption survey (1997, 97.5% for large portions), we anticipate that the ArfD will be exceeded by the intake through table grapes (149% and 277%, for the general population and children from 1-6 years old respectively).	

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

4. Environmental fate and behaviour (B.8)

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

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5. Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.9.1.3, Avian risk assessment	NL: For the estimation of residues on food items (Table B.9.1.3.2), the multiple applications should be taken into account (see SANCO/4145/2000 for MAF factors; these are based on a DT50 of 10 days, so they are applicable for folpet).	
(2)	Vol. 3, B.9.1.3, Avian risk assessment	NL: Values for daily food intake (Table B.9.1.3.3) are (much) lower than values in SANCO/4145/2000. It is not clear whether the values in Table B.9.1.3.3 are based on fresh or dry material; if based on dry, this should be corrected to fresh weight (generally a factor 30% is applied) and even then, values for herbivorous birds will be considerably lower than in SANCO/4145.	
(3)	Vol. 3, B.9.1.3, Avian risk assessment	NL would like to know where the assumption comes from that earthworms will contain 30% of PECsoil. Based on the logPow of 3.017 and the worst case Koc of 304, a BCFworm of 1.8 can be calculated, which is a factor 6 higher than the asumed 0.30.	
(4)	Vol.3, B.9.3.2, Risk assessment for mammals	NL does not agree with the assumption that multiple applications of folpet are not expected to increase the risk because of the rapid dissipation. The estimated DT50 in/on plants was 9.3 days, which does not exclude risk from multiple applications with an interval of 7 days. See also previous comment on avian risk assesment.	

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section 5 - Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(5)	Vol.1, List of Endpoints, Birds and mammals	NL: Please report all endpoints for birds and mammals in mg/kg bw/d.	Future risks assessments should be based on daily dose according to the guidance in SANCO/4145/EC.
(6)	Vol.1, List of Endpoints, Aquatic organisms	NL thinks it would be useful to include the 28-d semi-static fish study (Jenkins, 1999) in the List of Endpoints, to show that the risk from repeated acute exposure has been adressed.	
(7)	Vol.1, List of Endpoints, Aquatic organisms	NL thinks it would be useful to include the toxicity data on the metabolites in the LoE.	
(8)	Vol. 1, List of Endpoints, Effects on non-target arthropods	NL thinks a column with effect percentages should be added to the table 'Effects on non-target arthropods' in the List of Endpoints.	
(9)	Vol. 3, B 9.5.2, Risk to other arthropods	NL doesn't agree with the MAF factor of 1.5 which is used in the risk assessment. Looking at the MAF factors in Appendix III from ESCORT 2, it is clear that the MAF factor should be at least 2.0. Conform the formula in Gonzalez-Valero (1999), based on DT50 9.3 d and interval 7 d, a MAF factor of 2.4 can be calculated.	Formula for calculating the MAF factor: $MAF = (1-e^{-kni})/(1-e^{-ki})$ in which: k = ln2/DT50 i= interval (d) n = number of applications.
(10)	Vol. 3, B 9.5.2, Risk to other arthropods	NL: Could RMS please give a more elaborate argumentation on why adverse effects up to 69% after the last application on numbers of *T.pyri* in field studies are considered to show no unacceptable risk? From the summaries, NL cannot make up whether recovery takes place.	

section 5 - Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(11)	Vol. 3, B 9.5.2, and Vol. 1, Level 2, 3 and 4, Risk to other non-target arthropods	NL: Since there is a risk for *T.pyri* in the fisrt Tier, testing on more species is required. These tests are available, but with dosages much lower than the proposed application rates. NL agrees with the conlusion in Vol.1 that new studies are required, and wonders why this conlusion in Vol. 3 is not the same.	
(12)	Vol.3, B.9.6.3, Risk to earthworms	NL: Occurrence of the metabolite phtalamide in the earthworm test should be supported by measurements, but considering the low toxicity to aquatic organisms NL can agree with not asking for studies with the metabolite.	
(13)	Vol. 1, List of Endpoints, Earthworms	NL thinks the reproductive NOEC for earthworms should be included in the LoE.	
(14)	Vol. 1, List of Endpoints, micro-organisms	NL thinks it would be useful to report the tested concentrations in the LoE.	
(15)	Vol. 1, List of Endpoints	NL thinks endpoints for terrestrial plants should be included in the LoE.	

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

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

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, Listing of End Points, Identity	UK: The end points should list only 'relevant' impurities in the technical material, i.e. impurities of toxicological, environmental and/or other significance.	
(2)	Vol 1, Listing of End Points, Identity of relevant impurities	UK: Should this information be moved to the confidential information in Vol 4?	
(3)	Vol. 1, Listing of End Points, Methods of Analysis	UK: MoAs for impurities in the technical material should detail principle of methods only and not disclose details of identities of impurities.	
(4)	Vol. 3, B.5.2.2, MoA for animal tissues.	UK: A validated MoA was presented for these samples, but do we need to insist on an ILV given that intakes for animals are very low; is there likely to be a need for monitoring of animal products?	
(5)	Vol. 3, B.5.4, MoA for human fluids and tissues.	UK: The toxicological assessment does not seem to warrant a requirement for human fluids and tissues.	

2. Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.6.2.3, Acute inhalation toxicity	UK: Evidence of respiratory irritation was seen in this study (Cracknell, 1983); this finding is also consistent with the known mechanism of action of the breakdown product thiophosgene. Consideration should therefore be given to classification of folpet as 'Irritating to respiratory system' (R37).	
(2)	Vol. 3, B.6.2.5, Eye irritation	UK: We consider that the severity and irreversibility of the findings in the eye irritation study (Dreher, 1992c) warrant R41 classification.	
(3)	Vol.3, B.6.3.2, Short-term toxicity studies in the rat	UK: It is not considered possible to determine a NOAEL for the 90-day rat study (Reno, 1981), as histopathology was not performed on the stomachs of rats from the lower dose groups.	
(4)	Vol.3, B.6.4.2.2, *In vivo* genotoxicity studies in germ cells	UK: An additional published study (Collins, 1972a) reporting a positive result in a rat dominant lethal assay with folpet following oral and intraperitoneal dosing must be taken into consideration.	
(5)	Vol.3, B.6.4.3, Summary of genotoxicity studies	UK: A number of additional studies of the genotoxicity of folpet *in vivo* are available. These include a mouse spot test (negative), a mouse dominant lethal assay (negative, but concerns about the study quality) and the rat dominant lethal assay discussed above. All studies should be considered. The relevance of the tissues investigated in each study should also be considered, given the known rapid degradation of the folpet molecule and the likely reactive species.	

section 2 - Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(6)	Vol.3, B.6.4.3, Summary of genotoxicity studies	UK: Given the positive studies *in vitro* and conflicting *in vivo* data, we consider that further reassurance must be provided as to the genotoxicity of folpet in the mouse. An *in vivo* assay in the mouse gastro-intestinal tract, e.g. a comet assay, is considered to be preferable.	
(7)	Vol. 3, B.6.5.1, Long-term toxicity and carcinogenicity in the rat	UK: The endpoint used to determine the NOAEL in the study of Crown (1989) is considered to be appropriate; however the demonstrated decomposition of folpet in the diet should be taken into consideration. The NOAEL for this study is therefore calculated to be 190 ppm (equivalent to 12 and 16 mg/kg bw/d in males and females respectively).	
(8)	Vol. 3, B.6.5.1, Long-term toxicity and carcinogenicity in the rat	UK: The NOAEL in the rat carcinogenicity study of Crown (1985) is considered to be 500 ppm, based on hyperkeratosis of the forestomach epithelium at 1000 ppm.	
(9)	Vol. 3, B.6.5.2, Long-term toxicity and carcinogenicity in the mouse	UK: The NOAEL in the chronic mouse study of East (1994) is considered to be 150 ppm; the histopathological findings in the gastro-intestinal tract at 450 ppm are considered to be treatment-related.	
(10)	Vol. 3, B.6.6.2, Developmental toxicity in the rabbit	UK: The maternal NOAEL in the rabbit developmental study (Rubin, 1995) is considered to be 10 mg/kg bw, based on the slight initial reduced body weight gain at 40 mg/kg bw. Developmental effects however are not serious enough to warrant further investigation in either rat or rabbit, and might be expected given the level of maternal toxicity seen.	

section 2 - Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(11)	Vol.3 B.6.12, Dermal penetration	UK: The design of this study is sub-optimal as full-thickness skin was used. Additionally, 24-hour absorption following an 8-hour skin wash was not measured; figures for residual skin radioactivity and total recovery are not reported. It is therefore not possible to propose dermal absorption values of 1% from this study.	
(12)	Vol.3 B.6.10, Summary of mammalian toxicity	UK: Further reassurance as to the *in vivo* genotoxicity of folpet is required, as detailed above. Until additional data are provided, no safe level of exposure can be assumed.	
(13)	Vol.3 B.6.10, Summary of mammalian toxicity	UK: Further consideration of the toxicological significance of the metabolites phthalimide and phthalic acid and their potential inclusion in the residue definition is required.	
(14)	Vol.3 B.6.10.1, Acceptable Daily Intake	UK: The ADI should be derived from the lowest relevant NOAEL rather than just considering the NOAELs from the chronic toxicity studies. An ADI of 0.1 mg/kg bw/d can therefore be derived from the NOAELs of 10 mg/kg bw/d in the rat (Hobermann, 1983) and rabbit (Rubin, 1985) developmental studies and the 1-year dog study (Daly, 1986). A safety factor of 100 is appropriate.	This assumes the outstanding question of genotoxicity can be resolved
(15)	Vol.3 B.6.10.3, Acceptable Operator Exposure Level	UK: The AOEL can be derived from the NOAELs of 10 mg/kg bw/d in the rat and rabbit developmental toxicity studies. An AOEL of 0.1 mg/kg bw/d is therefore appropriate. Correction for oral absorption is not required, as folpet was found to be well absorbed (>75%) in the rat following oral dosing.	This assumes the outstanding question of genotoxicity can be resolved

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section 2 - Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(16)	Vol.3 B.6.11.3, Acute inhalation toxicity	UK: Based on the inhalation LC50 for folpet of 1.89 mg/l (Cracknell, 1993), the product should also be classified as 'Harmful by inhalation' (R20). Evidence of an irritant response was also seen in this study, therefore consideration should also be given to classification of the product as 'Irritating to respiratory system' (R37).	
(17)	Vol. 3, B.6.14.1, text below Table B.6.2.1.1.1: use of the UK predictive operator exposure model (POEM)	UK: The statement that 'the German model based on geometric mean values is considered appropriate for EC regulatory use' appears in PSD's guidance document for the German Model not the guidance document for the UK POEM as stated here. This guidance states that the accepted version of the German model (based on geometric mean values) should be used rather than the alternative version of the German model based on 75th percentile exposure values for EC evaluations. PSD has not suggested that the German model should be used in preference to the UK POEM. Therefore, the current version of the UK POEM (with exposure data for mixing and loading solid formulations) is an appropriate model to use (in addition to the German model) in this DAR.	
(18)	Vol. 3, B.6.14.1, Table B.6.2.1.1.1	UK: It is possible that grapevines may also be treated using hand-held sprayers.	
(19)	Vol. 3, B.6.14.1, exposure estimates for the use on grapevines.	UK: The EUROPOEM database has exposure values relating specifically to the use of tractor-mounted/trailed sprayers to treat grapevines. These data are more appropriate than those in the UK POEM or German models when considering this use.	

section 2 - Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(20)	Vol. 3, B.6.14.1, exposure estimates for glasshouse uses	UK: Although neither the UK POEM nor the German model have data relating to indoor uses, the EUROPOEM database contains studies on the use of hand-held equipment in glasshouses. Exposure estimates based on these data are likely to be more appropriate than those presented.	
(21)	Vol. 3, B.6.14.2, bystander exposure	UK: The bystander exposure estimate, based on published drift data, does not take into account inhalation exposure. It may be more appropriate to base this risk assessment on simulated bystander exposure studies which are available for orchard and field crops.	
(22)	Vol. 3, B.6.14.3.1, worker exposure	UK: Although it is stated that workers are not expected to enter treated cereal crops, this may occur (for example, for crop inspection or roguing activities). An estimate for this situation can be calculated using the German worker re-entry exposure model in conjunction with appropriate published transfer coefficients.	
(23)	Vol. 3, B.6.14.3, worker exposure	UK: As repeat applications can be made on all crops (with a maximum of 10 applications being supported on grapevines), an assessment of the risks to workers resulting from the build up of foliar residues would be useful, possibly based on the residue decline data mentioned briefly in this section.	

section 3 - Residues (B.7)

3. Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.7.3, Residue definition in plants	UK: Residue definition does not address therelevance of the metabolites: phthalimide and phthalic acid.	These are major metabolites in plants and their toxicological relevance and therefore relevance to the residue definition in plants does not appear to have been addressed.
(2)	Vol. 3, B.7.3, Residue definition in animals	UK: Is it necessary to set a residue definition in animals as data indicate it is unlikely any residue will be present?	
(3)	Vol. 3, B.7.15, Acute exposure assessment	UK: Acute risk assessment not complete. This is needed before the recommendation for Annex I listing can be assessed.	

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

4. Environmental fate and behaviour (B.8)

No comments

section 5 - Ecotoxicology (B.9)

5. Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	Vol. 3 Section B.9.1.1.3 b) Bobwhite quail reproductive toxicity study - determination of NOEC	UK: We would consider the small, but statistically significant, effects on mean body weight of hatchlings in all folpet treatments (at dietary concentrations of 100, 300 and 1000 ppm) of possible importance to survival in the wild, with the reproductive NOEC being < 100 ppm. .	This differs from that concluded in the DAR, where effects on body weight of hatchlings were not considered significant, with a concluded NOEC of 1000 ppm. Given this difference in interpretation, it is recommended that the matter is considered further at an EPCO Expert Working Group meeting.
(2)	Vol 3 Section B.9.1.3 Risk to birds:	UK: The calculated predicted residues of folpet in avian food items (Table B.9.1.3.2) assumes only one application at 1.5 kg a.s./ha, whereas the proposed GAP in vines relates to ten such applications at 7 day intervals. The estimation of residue levels in vegetation needs to take account of the effect of multiple applications. (e.g. by the use of a Multiple Application Factor, as in the non-target arthropod risk assessment, Vol 3, B 9.5.2), although it is accepted (as per current SANCO 2002 guidance) that insects will be exposed to one application	

section 5 - Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(3)	Vol 3 Section B.9.1.3 Risk to birds:	UK: The daily food intake values used in the risk assessment (Table B.9.1.33) for small, medium and large herbivorous birds and for small, medium, and insectivorous birds are much lower than that agreed in the SANCO (2002) risk assessment . Therefore the calculated TERs (Tables B.9.1.3.6-8) for birds under- estimate the risk and require re-calculating based on revised consumption levels and on food residue levels that take account of the use of multiple applications. Further consideration of the appropriate avian reproductive NOEC for use in the long-term risk assessment is also required. (as comment 1)	The daily food intake values used in the risk assessment (Table B.9.1.33) for small, medium and large herbivorous birds (equivalent to respectively 7.4%, 1.2% and 4.2 % of body weight) and for small, medium, and insectivorous birds (equivalent to respectively 29%, 13% and 7.4% of body weight) are much lower than that agreed in the SANCO (2002) risk assessment guidance (i.e. 76% and 44% of body weight for medium and large herbivorous birds respectively, and 104% of body weight for insectivorous birds). Also, the current guidance assumes medium sized (100g) birds consume 113g earthworms /day whereas the DAR assumes much lower levels of consumption. These large differences in intake estimates may partly be due to the use of dry weight consumption data, which should be corrected to wet weight before assessing maximum daily active substance intake values based on fresh weight residue estimates (the UK has previously used a conversion factor of x 2.4 for this).
(4)	Vol. 3 B.9.2.5 Risk to aquatic organisms:	UK: Given folpet's very rapid breakdown both in water and sediment (whole system DT50 of 0.018 days) we agree the use of the results from static (as opposed to flow through) studies is appropriate in the risk assessment.	
(5)	Vol. 3 Section B.9.3.1 Effects on other terrestrial vertebrates.	UK: We would consider the appropriate long-term NOAEL for use in the risk assessment was 250ppm (13.7-18.3 mg/kg bw/day) based on results of a two generation study in rats (Rubin Y 1986) where use at the next higher dose of 1500ppm (83.1-109.6 mg/kg bw/day) resulted in reduced pup weight during lactation and non-reproductive effects in the parents (hyperkeratosis of the oesophagus and forestomach).	We consider that a more detailed justification of the selection of the long-term toxicity endpoint for use in the environmental risk assessment is required, with the selection of the appropriate endpoint being confirmed at an EPCO Expert Working Group meeting.

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section 5 - Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(6)	Vol. 3 Section B.9.3.2 Risk to terrestrial vertebrates other than birds	UK: Maximum daily intakes for terrestrial vertebrates given in Table B.9.9.3.2.1 are under-estimates due to a lack of consideration of the effects of multiple applications on residue levels and use of inappropriate food intake values. The risk to terrestrial vertebrates therefore needs to be re-assessed, based on a comparison of corrected intake levels with the appropriate toxicity endpoint.	It is stated that exposure estimates for multiple applications 'are not considered to differ significantly from those based on a single application due to rapid dissipation of folpet in vegetation'. However, a foliar DT50 of 9.3 days has been estimated in Table B.9.1.3.4 (from 4 wheat residue trials) and multiple applications with a short application interval are proposed (e.g. use in vines of up to 10 applications with a 7 day minimum spray interval). Given the predicted foliar residue decline rate and short application interval, multiple applications are likely to significantly increase residue levels and this should be taken into account when estimating these levels (e.g. by use of an appropriate Multiple Application Factor as in the non-target arthropod risk assessment Vol 3. B.9.5.2). Intake values of 10% and 30% of body weight for large and small mammals have been assumed. However these intake values are based on dry weight consumption levels and must be converted to wet weight values before assessing maximum daily active substance intake values based on fresh weight residue estimates (the UK has previously used a conversion factor of x 2.4 for this).
(7)	Vol 3, B.9.5.2, risk to other arthropods	UK: Given the in-field risk to non-target arthropods identified in the tier 1 risk assessment for the proposed use in tomatoes and grapevines together with the significant reductions in *T pyri* reported in the grapevine field trials, Member States should consider the need for risk mitigation measures to protect non-target arthropod populations from the high dose uses.	We accept that there is potential for populations to recover following use of folpet and the lack of adverse effects reported in the lower application rate field trials indicates there is no need for mitigation measures for these uses. (eg wheat).

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

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

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

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section 2 - Mammalian toxicology (B.6)

2. Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.6.12, Dermal absorption	A: With respect to dermal absorption, there is an *in vivo* study* available (submitted for national registration in Austria) that is not evaluated in the DAR. As a result of this study (^{14}C-labelled Folpet has been applied), about 90 % of the applied dose were considered "absorbed" (based on amounts detected in excreta, carcass and in the skin). In the light of the results of this study, the proposed dermal absorption rate of 1 % (DAR) cannot be agreed upon. * Wilson, A.S.: A Study of Dermal Penetration of ^{14}C-Folpet in the Rat, [redacted] Toxicol Study No. MAG/1/PH; 17.10.1990	

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section 3 - Residues (B.7)

3. Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	Vol. 1, 2.4.4, Proposed EU MRLs and compliance with existing MRLs	AT: There are no currently EU-MRLs for cereals; 0.1 mg/kg for other products according to Directive 1976/895/EEC does not include cereals	
(2)	Vol. 3, B.7.15, acute exposure	AT: considering the subsequently proposed ARfD of 0,1 mg/kg bw, the use of folpet in table grapes should be reconsidered.	Using the UK model for the determination of the acute intake, for toddlers the ARfD will be exceeded by 212% (using the HR of SEU 3.9 mg/kg).
(3)	Vol. 1, list of endpoints, summery of critical residues data, page 64	AT: editorial advice: due to the formatting of page 64, the last two columns of the table “Summery of critical residues data (Annex IIA, Point 6.3) are missing in the hardcopy	

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

4. Environmental fate and behaviour (B.8)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, List of endpoints, PEC surface water	AT: Concentration unit for PEC_{sw} is missing. Information about concentration of major metabolites is missing.	
(2)	Vol. 1, List of endpoints, Classification and proposed labelling	AT: Classification and labelling with regard to fate and behaviour data are missing.	

5. Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	Vol. 1, List of endpoints, Toxicity data for aquatic species	AT: Volume 1, page 36 is stated ”The major metabolites of folpet were much less toxic to aquatic organisms…”, however no toxicity data for major metabolites and related TER values are mentioned in list of endpoints.	
(2)	Vol. 1, List of endpoints, Classification and proposed labelling	AT: Classification and labelling with regard to ecotoxicological data are missing.	

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(3)	Vol. 3, B.9.5.2, Risk assessment to non-target arthropods	AT: The field studies on *T. pyri* do not sufficiently address the maximum intended use of 10 appl.s of 1.5 kg ai/ha. Only 8 appl.s have been investigated and the potential effects of 2 further appl.s can not be predicted. Furthermore the first appl.s in all trials were performed with rates significantly lower than 1.5 kg ai/ha and therefore a more pronounced initial damage to the population can be expected. According to Escort 2, where the in-field HQ > 2 one additional species has to be tested. For folpet, additional species have been tested with only one third of the intended single rate. In our opinion the multiple appl. scenario should also be addressed for one additional species. The HQs for *A. rhopalosiphi* have been calculated based on a LD50 figure which is derived from an extended lab study. As the HQ trigger has been validated for artificial substrate, it should at least be indicated that the HQs for *Ar* should be regarded as “tier 2” figures. The data provided are not sufficient to support acceptability of effects on nta`s.	

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(4)	Vol. 3, B.9.6.3 and Vol. 1, List of endpoints, Effects on earthworms	AT: According to the GAP Folpet is applied up to 10 times per season in grapes. Sublethal effects on earthworms have to be tested if the number of applications is >6, regardless of persistence (GD Terrestrial Ecotoxicology). Although otherwise stated in Volume 1 of the DAR, an earthworm reproduction study was conducted (see Vol. 3 of DAR). In this study a NOEC of 5.2 mg ai/kg soil was determined. To account for potential toxicity in soils with lower amounts of organic matter than the artificial substrate used in toxicity studies, this number is divided by a factor 2 (EPPO). The PECmax was determined to be 1.478 mg ai/kg soil (50% interception) or 0.887 mg/kg (70% interception). NOECcorr. = 2.6. Thus TERlt is either 1.76 (assuming 50% interception) or 2.9 (assuming 70% interception). In both cases the Annex VI trigger of 5 is not met and save use for the application in vine not proven.	

section 2 - Mammalian toxicology (B.6)

2. Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, Level 2, 2.1.4, Classification and labelling	SE: Cancer category 3 would be added, according to the List of classification and labelling (ref: Annex I of Directive 67/548/EEC)	

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

4. Environmental fate and behaviour (B.8)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.8.6 and Vol 1, list of endpoints, PEC in groundwater	SE: Please clarify what input values - DT50 and Koc - in the final PECgw simulation for FOCUS EU scenarios, for folpet and all metabolites. For Phthalic acid och Phthalamic acid, it is stated (in B.8.2.1) that the Koc were estimated by EWIWIN program but the results are not presented.	
(2)	Vol. 3, B.8.9 Definition of the residue	SE: We agree to include only folpet in the definition of residues in soil and in aquatic systems. However, as justification for excluding the metabolites, please also refer to the ecotoxicological studies available. Before concluding on the definition of the residues in groundwater, the input values used for metabolites needs to be clarified.	

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5. Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.1.3 Risk assessment for birds	SE: The short term and the long term risk assessments for birds are based on the dietary concentrations. According to the guidance document the toxicity endpoint should be expressed as daily dose (mg as/kg bw per day), in order to take into account the different feed intake between laboratory and wild animals. We suggest this minor change should be adopted also for substances at the 2nd stage of the review programme. The difference in feed intake depends mainly on different energy expenditure of the animals, and on different energy and moisture content of the food in the laboratory compared to that in the field.	

section 5 - Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(2)	Vol 3, B.9.3.2. Risk assessment for wild mammals	SE: The short term and the long term risk assessments for mammals are based on the dietary concentrations. According to the guidance document the toxicity endpoint should be expressed as daily dose (mg as/kg bw per day), in order to take into account the different feed intake between laboratory and wild animals. We suggest this minor change should be adopted also for substances at the 2nd stage of the review programme. The difference in feed intake depends mainly on different energy expenditure of the animals, and on different energy and moisture content of the food in the laboratory compared to that in the field. In addition, we suggest it be considered to use the NOEL of 10 mg/kg bw/d from teratology study in rabbit as a basis for the short-term risk assessment since the effects described in B.6.6.3 appear to be relevant.	

section 5 - Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(3)	Vol. 3, B.9.2.5, Risk assessment for aquatic organisms	SE: We do not agree to the suggested use of probabilistic risk assessment approach and the suggestion to disregard any potential interspecies difference in sensitivity. These approaches should be discussed and agreed upon before they are used as a basis for conclusion, thus we should await the outcome of the EUFRAM project. We suggest that conclusions should be drawn only from the first part of the risk assessment presented, indicating that risk mitigation (e.g., spray free zone of 20 m) is warranted.	

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

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

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

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section 2 - Mammalian toxicology (B.6)

2. Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	B.6.4.3.1 Genotoxicity	DK consider classification for genotoxicity. Folpet induces a wide range of genotoxic events in vitro including gene mutations/DNA damage in bacteria and mammalian cells, chormosomal aberrations in mammalian cells and mitotic recombination in yeast (not present in DAR). Although folpet was active in both the +/- S9 activation, the response was generally more pronounced without S9 activation.	
(2)	B.6.5.3 (Long time toxicitity)	DK suggest classification for carcinogenecity. Based on the increased incidences of adenomas and carcinomas in the duodenum of male and female mice in two strains (CD-1 and B6C3F1). The highly reactive thiophosgene is most likely the metabolite responsible for duodenal tumor formation in mice. In rats, folpet was classified as a carcinogen in males based on an increase in the incidences of C-cell adenomas and carcinomas of the thyroid as well as interstitial cell tumors of the testes. There was no evidence of duodenal tumors in the rat; however, there was a dose related increase in incidence and severity of hyperkeratosis of the esophagus and stomac which may be due to thiophosgene.	The increase in the incidence of duodenal adenocarcinomas in the CD-1 mouse study occurred at relatively high doses. A similar response was observed in a 2-year feeding study with B6C3F1 mice.

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section 2 - Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(3)	B.6.6.4 Reproducitive toxicity	DK suggests classification for developmental toxicity. Folpet caused an increase in the incidence of hydrocephaly in fetuses with associated domed skull and irregularly-shaped fontanelles in NZW rabbits in the presence of maternal toxicity. Both fetal and litter incidences of this malformation were increased. There was also evidence of fetal effects (delayed ossification of the sternebrae) in rabbits at a lover dose than that causing maternal toxicity.	

section 2 - Mammalian toxicology (B.6)

3. Residues (B.7)

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

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

4. Environmental fate and behaviour (B.8)

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

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5. Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
	Vol.3 Section B.9.1.3.Risk to birds.	DK: The daily food intake in Table B.9.1.33 (stated to be according to the SANCO 2002 risk assessment) for small, medium and large herbivorous birds and for small, medium insectivorous birds is very low. This does not seem to be correct.	
	Vol. 3.Section B.9.3.1. Effects on other terrestrial vertebrates (mammals)	DK: Concerning the risk assessment for mammals based on the results from the two generation study in rats (Y. Rubin 1986) we suggest to use 250 ppm in stead of 1500 ppm for the long-term risk assessment. A food content of 1500 ppm reduced the pup weight and caused hyperkeratosis (a thickening of the epidermis cells) in the stomach of the parents.	

Proposed decision with respect to the application for inclusion of the active substance in Annex I

Comment on the proposed decision of the Rapporteur Member State

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, Level 3, 3.2: Proposed decision concerning inclusion in Annex I	DE: Germany does not agree with the proposal of the RMS Italy to include the active substance folpet in Annex I of Directive 91/414/EEC. The data submitted for aquatic and terrestrial non target organisms are considered insufficient for a final risk assessement.	

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

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

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.5.2.1 Analytical methods (residue) for plant material	DE/Statement: . The standard multi-residue method DFG S-19 has been adequately validated for applications to plant products. It is tested in interlaboratory tests for dry and water content samples. Results are published in the Collection of Official Methods under Article 35 of the German Federal Food Act (method L 00.00-34)	
(2)	Vol. 3, B.5.3.2 Analytical methods in water	DE/Statement: A method for residues in surface water is not required because of the low stability of Folpet (DT90 < 1 day)	
(3)	Vol. 3, B.5.3.3 Analytical methods in air	DE/Data Requirement: For determination of Folpet in air a confirmatory method is missing and should be provided.	

2. Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	Vol. 1, 2.1.4, Classification and labelling	DE: In accordance to the 28th Time Council Directive 67/548/EC, folpet has to be classified and labelled for toxicological properties as follows: Xn; R20-36-40-43. The risk phrase R40 is necessary because of the clear neoplastic effect in mice and must be amended, therefore.	Note: For the classification and labelling of the preparation the risk phrase R 40 should also be considered into account.
(2)	Vol. 1, 3.1, Background to the proposed decision, paragraph on classification and labelling	DE: Indeed, folpet is classified as "Harmful by inhalation". However, the appropriate risk phrase is not R22 but R20.	
(3)	Vol. 1, 2.3.2 and Vol.3, B.6.10.1, ADI	DE: Proposal: An ADI of 0.1 mg/kg bw is suggested, based on the NOAEL of 10 mg/kg bw/d in the 12-month dog study and supported by the NOAELs obtained in the long-term and multigeneration rat studies and the developmental toxicity study in rabbits.	In principle, the proposed ADI of 1.25 mg/kg bw that was established on the basis of the NOAEL (ca 12.5 mg/kg bw/d) in the long-term study in rats could be agreed with, too. However, this numeric value would be (1) higher than the proposed ARfD of 0.1 mg/kg bw, and (2) higher than the ADI suggested for the closely related compound captan although the definition of residues comprises both active ingredients ("sum of captan and folpet"). A slightly lower ADI of 0.1 mg/kg bw would be also in compliance with the conclusions of the 1995 JMPR.
(4)	Vol. 1, 2.3.4 and Vol. 3, B.6.10.3, AOEL	DE: Proposal: An AOEL of 0.1 mg/kg bw is suggested, based on the NOAEL of 10 mg/kg bw/d in the 12-month dog study and supported by the NOAELs obtained in the developmental toxicity study in rabbits.	The numeric value is slightly lower than proposed by the RMS. However, the AOEL should be derived from so-called mid-term studies. Taking this approach, the subchronic dog study and the rabbit teratogenicity study appear to be best-suited.

section 2 - Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(5)	Vol. 1, 2.3.6, Impact on human and animal health	DE: The numeric value of the suggested systemic AOEL [0.1 mg/kg bw/d (4)], is slightly lower than proposed by the RMS [0.125 mg/kg bw/d]. A new risk assessment would not be needed.	Also with a systemic AOEL of 0.1 mg/kg bw/d, no risk would be anticipated under the proposed conditions of use, even without PPE (German model)

section 3 - Residues (B.7)

3. Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.7.12, Proposed Eu MRLs	DE: Based on UK consumption data and an ARfD of 0.1 mg/kg bw the proposed MRLs for tomato and grapes exceed the ARfD for toddlers. Tomato (var.factor 7): 125 %; Grapes (var.factor 5): 272 %. An acute dietary risk assessment must be made before an inclusion into Annex 1 can be proposed.	

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

4. Environmental fate and behaviour (B.8)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, Point 2.5.3, Fate and behaviour in water and Vol. 3, Point B.8.4.4, Water sediment studies	DE: Considerable amounts of bound sediment residues of approx. 25% AR were detected 7 and 14 days after application of folpet. After 100 days, the residues decreased to approx. 10 %. Since folpet (1.5 kg a.s./ha) might be applied up to 10 times with weekly intervals, it is assumed that the bound residues will accumulate due to multiple application. This issue should be addressed in the discussion to this chapter and might also be of relevance in the risk assessment for aquatic compartment including the sediment dwelling organisms.	The importance of this comment might increase, if it would be demonstrated that a large portion of the bound residues is still related to the parent compound that can be mobilised and/or taken up by sediment dwelling organisms.

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

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(2)	Vol. 1, Point 2.5.3, Fate and behaviour in water and Vol. 3, Point B.8.6, PEC in surface water and in ground water	DE: PEC calculations for surface water and sediment according to the Guidance Document on Aquatic Ecotoxicology (Sanco/3268/2001 rev.4 (final)) from October 17th, 2002, i.e. using the current FOCUS surface water modelling tools might yield more reliable data on the concentrations in sediment.	Loading to surface water via spray drift was calculated using the spray drift tables of Ganzelmeier et al. (1995). PEC sediment values were not reported due to the rapid degradation of folpet in surface water. For the same reason, runoff and drainage were not considered for the parent compound. PEC surface water values for metabolites were calculated assuming a runoff event of 0.5 % of the applied product entering a standard water body 3 days after application. Since some essential input parameters and assumptions are different in the FOCUS models, the use of the current FOCUS software (FOCUS Steps 1-2 and FOCUS SWASH) would lead to different PEC values. At least at FOCUS-Step1/2 level, the PEC values are expected to be higher than those presented in the DAR. MS should discuss, whether the available information on the fate of the compound in water/sediment might justify the additional use of FOCUSsw steps 1-2 for PEC calculation, even though they are usually not applied to second list compounds.
(3)	Vol. 1, Appendix 3, Listing of endpoints	DE: In the table on PEC surface water (p. 70) no units are given. In the table on PEC sediment (p. 70) no values are reported (see comment No. 1 and No.4). In the table on toxicity data for aquatic species (p. 72) effect concentrations are given in mg/L, but the EAC appears in µg/L. Consistent reporting of units would be preferable.	
(4)	Vol. 3, Point B.8.4.4, Water sediment studies	DE: The first sentence is not complete (“The degradation… was investigated… in accordance…” with?).	

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section 5 - Ecotoxicology (B.9)

5. Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	Vol.3, Point B. 9.1.3, Risk to birds	DE: It might helpful, if the ERA for birds would be presented according to the Working Document SANCO/4145/2000.	The use of the interception factor should be justified. This is of particular importance since the interception factor for fungicides is 0.4 according to SANCO/4145/2000. Furthermore, not only secondary poisoning from fish to fish eating birds but also from earthworm to earthworm eating birds should be presented.
(2)	Vol.1, Point 2.6.2, Effects on aquatic species and Vol. 3, Point B.9.2.5, Risk to aquatic organisms	DE: A higher-tier risk assessment based on an EAC is presented. A Tier-1 risk assessment including the calculation of TERa and TERlt values as required by the Guidance Document on Aquatic Ecotoxicology (Sanco/3268/2001 rev.4 (final), 17 October 2002) should be conducted and reported prior to a higher-tier risk assessment.	According to the Guidance Document on Aquatic Ecotoxicology (Sanco/3268/2001 rev.4(final), 17 October 2002) an EAC is estimated for the refined risk assessment, taking into account the overall evaluation of the compound in the aquatic compartment.

section 5 - Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(3)	Vol.1, Point 2.6.2, Effects on aquatic species and Vol. 3, Point B.9.2.5, Risk to aquatic organism	DE: a) The higher-tier risk assessment is based on an EAC of 9.8 µg/L which is derived from the most sensitive fish species (LC50 of 98 µg/L for brown trout). b) Since chronic effects on fish are not covered by this approach, it is recommended to base the risk assessment on the NOEC value from the 28-day chronic toxicity test with rainbow trout. c) A safety factor of 5 should be applied to the NOEC (resulting in approx. 4 µg a.s./L) with respect to the uncertainty due to inter-species sensitivity distribution and possible effects in fish life cycle which are not covered by the ELS test. d) PECmax surface water values derived by current FOCUS modelling tools might be used for the risk assessment.	a) The use of an EAC in the risk assessment based on a LC_{50} instead of a NOEC from chronic toxicity testing is reasoned by the RMS with a static test approach to be more realistic than a flow-through system due to the rapid hydrolysis of folpet in the water phase. b) Since folpet might be applied several times (up to 10 x 1.5 kg a.s.s/ha) in weekly intervals, the semi-static approach from the prolonged toxicity study with rainbow trout (12 applications in total with 2-3 days intervals) is believed to be more realistic and to cover the chronic risks for fish. c) Inter-species sensitivity distribution investigated in acute tests with several fish species showed a factor of about 2.5. Additionally, as described in the literature, a factor of approx. 2 can be assumed from comparison of the endpoint sensitivity of fish life-cycle (FLC) and early life-stage (ELS) tests. d) Since the NOEC values from the cited fish study are based on nominal concentrations, TER calculations should be performed with PECmax values.
(4)	Vol.1, Point 2.6.2, Effects on aquatic species and Vol. 3, Point B.9.2.5, Risk to aquatic organism	DE: It should be reconsidered if it is reasonable to estimate an ecologically acceptable concentration EAC which is based on acute effects on one group of organisms (fish) only. Since the toxicity of folpet to daphnids is not much different compared to the toxicity against fish, it is doubted that this EAC covers possible risks to the whole aquatic community.	See comment No. 2 In order to reduce the uncertainty of potential effects on the aquatic community and to derive a reliable EAC, the performance of a semi-realistic multi-species effect study would be helpful.

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section 5 - Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(5)	Vol. 1, Point 2.6.3, Effects on bees and other arthropod species and Vol. 3, Point B.9.5, Effects on other arthropod species	DE: The RMS states that "there are serious doubts that the available studies could be used for risk assessment". This statement is strongly supported since all presented studies (laboratory as well as field) did not use the highest application rate or the highest number of applications.	Despite the clear statement cited from Vol. 1 in Column 2, the RMS states in Vol. 3, Point B.9.5 that the formulation Folpan 80 WDG fulfils the criterion for the authorisation. This seems to be a contradiction. For an ERA according to ESCORT II, new data are necessary as recommended by the RMS in Vol. 1.
(6)	Vol. 1, Point 2.6.4, Effects on earthworms and other soil macro-organisms	DE: According to Vol. 1, Point 2.6.4 as well as to the Listing of Endpoints (Appendix 3), only earthworm acute tests were performed. This is not sufficient, since an earthworm reproduction test must be performed if the number of applications is higher than 6 (irrespective of persistence).	In Vol. 3, the results of a reproduction study with a formulation are given. (According to this study, the TER_{lt} is clearly below 5 (3.5; assuming 50% crop interception) or just above 5 (5.8; assuming 70% crop interception). It is not acceptable to use different ground cover values in different parts of the DAR.)
(7)	Vol. 1, Point 2.6.5, Effects on soil micro-organisms	DE: The RMS states that the highest rate tested is 65 times higher than the PECsoil. In fact this ratio is only 14 times higher (21.24 mg a.s./kg / 1.48 mg a.s./kg = 14.4). However, this mistake does not have an impact on the outcome of the ERA.	
(8)	Vol. 1, Point 2.6.6, Effects on other non-target organisms (flora and fauna) and Vol. 3, Point B.9.9, Effects on other non-target organisms believed to be at risk	DE: The risk of folpet to plants was assessed using field screening tests. These studies are not well documented (e.g. the test species are not given in all cases). In addition, it is stated by the RMS that the basic requirements of OECD Guideline 208 are fulfilled which is not the case (this guideline covers only laboratory or glasshouse tests). In addition, only single applications were used.	

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section 5 - Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(9)	Vol. 3, Point B.9.4, Effects on bees	DE: In order to avoid confusion the correct abbreviation “HQ” (Not QHC) should be used throughout the text.	
(10)	Vol. 3, Point B.9.5, Effects on other arthropod species	DE: In Table B.9.5.1.9, in the control column at day 8, a CR is given of 42%. However, it is impossible by definition to give a CR here.	

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

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

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	General	EFSA: It should be noted that references of studies which are unacceptable or not necessary in the light of Directives 94/37/EC and 96/46/EC (Annex IIA and IIIA of 91/414/EEC) should be removed from the chapter "References relied on", because it is not possible to rely on these references.	
(2)	Vol. 1, p. 6, 1.3.9 Specification of purity of the active substance	EFSA: It should be noted that the minimum purity of the active substances can not be regarded as confidential.	
(3)	Vol. 1, p. 52, List of endpoints, FAO specification	EFSA: For clarification, the acceptable deviation of ± 20 g/kg from the declared content should be mentioned.	
(4)	Vol. 1, p. 53, List of endpoints, Boiling point/temperature of decomposition in relation to Volume 3, B.2	EFSA: The given argumentation is not applicable. According to Directive 94/37/EC the measurements has to be carried out up to 360 °C. Therefore, it should be indicated in the list of endpoints, that data are required (e.g. as open point).	
(5)	Vol. 1, p. 53, List of endpoints, relative density in relation to Vol. 3, B.2.1.4	EFSA: It should be clarified whether the relative density or the density was determined.	

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

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(6)	Vol. 1, p. 56, List of endpoints, Summary of intended uses	EFSA: For transparency and better comprehensibility, instead of the "summary of intended uses", the list of representative uses evaluated, as mentioned in EPCO Manual E4, should be used.	
(7)	Vol. 3, p. 15ff, Table B.2.2.1 Summary of the physical and chemical properties of the plant protection product	EFSA: Clarification is needed regarding the properties where more than one batch is mentioned. Does this mean that the tests were performed for all the mentioned batches?	
(8)	Vol. 3, p. 19, B.2.2.8 Flowability	EFSA: More information is needed to assess whether the remained residues after 20 liftings are acceptable or not.	
(9)	Vol. 3, p. 34, B.4 Proposals for classification and labelling	EFSA: For transparency and better comprehensibility, a justification for the proposed classification and labelling should be given.	
(10)	Vol. 3, p. 35, B.5.1 Analytical methods for formulation analysis	EFSA: A statement concerning the applicability of CIPAC method(s) is missing.	
(11)	Vol. 3, p. 35ff, B.5.2.1 Plants, plants products and B.5.2.2 Animal tissues and milk in relation to Volume 1, Level 4	EFSA: The assessment of the analytical methods for the determination of residues in food should be discussed in an expert meeting. According to the mentioned methods and issue-related information, it seems to be that sufficient data/methods are available or not necessary.	

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

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(12)	Vol. 3, p. 45, B.5.3.2 Analytical method in water	EFSA: The argumentation for the non submission of an analytical method for the determination of residues in surface water is not acceptable. A validated analytical method must be submitted also for surface water, due to the fact that in general the matrix surface water is less clean than drinking water. However, taken issue related information into account, the need for an analytical method is maybe questionable. This should be discussed in an expert meeting.	
(13)	Vol. 4, p. 4, 1.8 Method of manufacture	EFSA: It seems to be that information regarding the purity and source (commercially available or not) of the starting material are missing.	
(14)	Vol. 4, p. 11, Table 1.11-2 Folpet technical composition statement	EFSA: Clarification it needed concerning the given maximum levels for the impurities. Some of the specified limits are not reliable according to the submitted batch analyses. A new specification or a justification for the mentioned values should be required. According to the presented data, it seems to be that no different batches were used for the toxicological and the ecotoxicological studies. Therefore it must be confirmed that a specified limit above the maximum value found in the batch analyses is acceptable.	

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

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(15)	Vol. 4, p. 12ff, 4.1.2 Methods for the determination of significant and/or relevant impurities	EFSA: Data to confirm the identity of the impurities revealed by chemical analysis must be provided to address the requirement of the Directive on the specificity of the method(s).	

2. Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol.3. B.6 General comment	EFSA: The results in the studies are sometimes poorly described. There is a lack of informative tables and/or the effect as % of control and if it as NOEL or a NOAEL value. The concentration of the compound is often presented in ppm without demonstrating the corresponding value in mg/kg bw/day. Furthermore, the conclusions are very brief and in some cases even lacking. The provision of an addendum where more information is provided, for instance for the studies being considered as crucial for setting of ADI, AOEL and ARfD, would be appreciated in order to increase understanding and transparency. Proposed studies are: B.6.3. one year dog study (Daly 1986) B.6.5. 2-year rat study (Crown, 1989) B.6.6. 2-generation reproduction, rat (Rubin, 1986) B.6.6. teratogenicity study, rabbit, (Rubin 1985c)	
(2)	Vol.3. B.6.6. Developmental toxicity	EFSA: There seems to be evidence of teratogenic potential of folpet at maternal non-toxic doses both in rat and rabbit. Thus, classification of R63 is proposed.	

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section 3 - Residues (B.7)

3. Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, level 3, 3.2 Proposed decision concerning annex I inclusion	EFSA: We note that an annex I inclusion is proposed although a complete risk assessment for the safety of the consumer is not yet achieved. Acute risk assessment is still to be done and no data are at this stage available concerning the effect of processing on the nature of residues.	
(2)	Vol. 1, level 4, 4.7, Further residue data needed	EFSA: We agree with the data requirements proposed by RMS, namely • Two greenhouse trials for tomato • A hydrolysis study, in representative hydrolytic conditions • A whole balance study for tomato washed, peeled and canned or used for juice, 3 follow-up studies in juice and canned tomato.	
(3)	Vol. 3, B.7.1.a) Metabolism study in winter wheat	EFSA: There is a discrepancy between the results of the metabolism study and residue trials as far as the a.s. is concerned. In the metabolism study folpet was identified at a level of 8.56 mg/kg while its highest amount in residue trials was 0.13 mg/kg, with very similar rates of application. Can an explanation be given?	

section 3 - Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(4)	Vol. 3, B.7.1.b) Metabolism study in grapes	EFSA: In fruits, identified compounds and unknown 1 accounted for 85.88% of the TRR, while the rinsate and plant extracts represented in total 98.51% of the radioactivity. Is there an explanation for this apparent loss of radioactivity?	
(5)	Vol. 3, B.7.2 Metabolism in livestock	EFSA Indication of the label position in the case [trichloromethyl-^{14}C] folpet seems not correct.	
(6)	Vol. 3, B.7.2 Metabolism in livestock	EFSA: The exposure rate of the animals in both goat studies should be expressed in mg/kg bw as well to allow easier comparison with the expected exposure level calculated from the amount of residues in feedingstuffs.	
(7)	Vol. 3, B.7.3 Residue definition	EFSA: Proposed residue definitions are understood as relevant for monitoring. With regard to the amount of metabolites present in the metabolism studies, the residue definition for risk assessment and the need for conversion factor(s) should be addressed.	
(8)	Vol. 3, B.7.3 Residue definition	EFSA: In products of animal origin, folpet cannot be considered as a valid indicator of the residue situation.	
(9)	Vol. 3, B.7.6.1 Residue trials in tomatoes	EFSA: Considering the fact that the storage stability of residues on tomatoes is weak, the freezer storage duration should be explicitly mentioned for tomatoes as key point of the acceptability of the trials.	

section 3 - Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(10)	Vol. 3, B.7.12 Proposed MRLs	EFSA: the reason why the result at 0.13 mg/kg in wheat was disregarded for MRL proposal is not mentioned in the DAR.	
(11)	Vol. 3, B.7.15 Estimates of dietary exposure	EFSA: Acute intake calculations have not been carried out.	

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

4. Environmental fate and behaviour (B.8)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol 1. List of end points. Mineralisation after 100d. p. 65.	EFSA: Preferably only mineralization form phenyl labelled folpet should be given of label position ot be indicated.	
(2)	Vol 1. List of end points. Rate of degradation in soil.	EFSA: Please include number of studies and range of r^2. Specify kinetic model. Specify parameters used for FOCUS modelling (mean or median DT_{50} normalised to 1okPa of pF2, 20oC with Q10 of 2.2).	
(3)	Vol 1. List of end points. PEC soil. Method of calculation.p. 67	EFSA: Please, indicate here kinetic used, soil depth, soil density and DT_{50}. Detailed formulas should preferably be removed from the list of end points.	
(4)	Vol 1. List of end points. Distribution in w/s system.p.69 (active substance).	EFSA: It should be stated clearly if folpet is found in the sediment compartment.	
(5)	Vol 1. List of end points. Distribution in w/s system.p.69.	EFSA: Preferably, indicate maximum amount of each metabolite in water and sediment phases.	
(6)	Vol 1. List of end points. PEC ground water. p. 70.	EFSA: Please indicate the model used for FOCUS modelling, the crops and if the nine scenarios have been considered.	
(7)	Vol 3. B8. General.	EFSA: Acceptability and relevance of each study should be given.	
(8)	Vol 3. B8. General.	EFSA: Reports are generally poorly quoted in the main text. In some sections, reports are not quoted at all. Please, amend.	

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

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(9)	Vol 3. B.8.1.3 Field studies.	EFSA: Field soil degradation studies should not be considered essential since: 1) there are not required by the directive in this case, 2) are not necessary to refine risk assessment and 3) do not reflect the fate of folpet under European field conditions. (Note for the list of essential studies).	
(10)	Vol 3. B.8.1.4. Summary and assessment. Table B.8.1.4.1.	EFSA: R^2 should be indicated for each determination. Normalised DT_{50} to 1okPa of pF2, 20oC with Q10 of 2.2 should be calculated for FOCUS ground water modelling.	
(11)	Vol 3. B.8.1.4. Summary and assessment.	EFSA: Degradation of the thio(trichloromethyl) side chain is addressed with some studies of the active substance captan. These studies should be properly summarised and included in the list of references relied on. Formation of thiophosgene should be assessed.	
(12)	Vol 3. B.8.2.1. Adsorption / desorption.	EFSA: Acceptability of EWIWIN program to determine Koc of folpet metabolites should be discussed and justified.	
(13)	Vol 3. B.8.4.4. Water sediment studies.	EFSA: The underlaying kinetics under the ”computerized statistical model” used to calculate the degradation parameters should be given.	
(14)	Vol 3. B.8.6. PEC ground water.	EFSA: The input parameters used for FOCUS ground water simulations and the rationale for their selection should be given in the DAR.	
(15)	Vol 3. B.8.6 PEC surface water.	EFSA: PEC surface water for the metabolites should be provided.	

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

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(16)	Vol 3. P.8.6. PEC sediment.	EFSA: PEC sed should be provided for the metabolites.	
(17)	Vol 3. B.8.7.	EFSA: Thiophosgene should be considered for the residue definition in air.	
(18)	Vol 3. B.8.10. References relied on.	EFSA: Please revise the list. Some studies are missing, e.g. Annex III studies.	

section 5 - Ecotoxicology (B.9)

5. Ecotoxicology (B.9)

No comments are available at this stage.

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

4. Environmental fate and behaviour (B.8)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol.1, list of end points, soil adsorption studies	SI: Please give the average/median value for the Koc as requested according to the guidance for the end point list.	
(2)	Vol.1, list of end points, distribution in water-sediment systems (metabolites)	SI: Please mention maximum % in which individual metabolites were found in water phase and sediment phase.	
(3)	Vol.3, B.8.2.1 Adsorption and desorption	SI: The value of 1/n is too low for the loam soil (EUROSOIL 3) and sand soil (LUFA 2.1) in the study of Geffke, 2000. This means that adsorption/desorption behaviour is not adequately described by the Freundlich theory. Corresponding Koc values should not be further considered in the risk assessment.	

section 5 - Ecotoxicology (B.9)

5. Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(1)	Vol. 1, list of end points, effects on terrestrial vertebrates	SI: Please report LC50 and NOEC for birds and NOEC for mammals also as daily as these are the end points to be used according to the final guidance.	
(2)	Vol. 1 List of end points, effects on other terrestrial arthropods	SI: Please mention the effect percentages in the table.	
(3)	Vol. 1 List of end points, effects on earth worms	SI: The reproductive end point and the long term risk assessment for grapes should be included.	
(4)	Vol. 1 List of end points, effects on other non-target organisms	SI: The test results with non-target plants should be included.	
(5)	Vol.3 B.9.1.3. Risk to birds	SI: The risk assessment is not in line with the final guidance document. Please make clear which version of SANCO/4145 was used.	
(6)	Vol. 3 B.9.2.1.1 Fish	SI: According to the summaries the lower test concentrations were below the limit of quantification (102 µg/L). This has to be clarified.	It is impossible to conclude on an end point if test concentrations cannot be adequately measured. It is not clear if initial concentrations in these media were >80% of nominal.
(7)	Vol.3 B. 9.5.2. Risk to other arthropods	SI It is not appropriate to use the trigger of 2 in combination with an extended laboratory study on *Aphidius*.	The trigger of 2 for the Hazard Quotient is validated for worst-case tests with exposure on glass plates and not for extended laboratory tests.
(8)	Vol.3 B.9.6.3 Risk to earthworms	SI We consider it more appropriate to use 50% interception as realistic worst case in grapes for the long-term risk assessment.	

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