PEER REVIEW REPORT ON **MYCLOBUTANIL** 07.05.2007

TABLE OF CONTENTS

Comments on the Draft Assessment Report on myclobutanil (EAS)

RMS BE

End of commenting period: 31.05.2006 (NOT), 31.05.2006 (MS)

Date	Supplier	File
24.05.2006	Germany	01 myclobutanil comments DE 2006-05-24.doc
25.05.2006	The United Kingdom	02 myclobutanil comments UK 2006-05-25.doc
30.05.2006	The Netherlands	03 myclobutanil comments NL 2006-05-30.doc
30.05.2006	Dow Agroscience	04 myclobutanil comments NOT 2006-05-30.doc
31.05.2006	Poland	05 myclobutanil comments PL 2006-05-31.doc
31.05.2006	Austria	06 myclobutanil comments AT 2006-05-31.doc
01.06.2006	Denmark	07 myclobutanil comments DK 2006-06-01.doc
21.07.2006	EFSA	08 myclobutanil comments EFSA 2006-07-21.doc

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, IIA 2.8, partition coefficient	DE: The study indicating a log Pow of 2.56 was actually not accepted by the RMS. Since the log Pow appears to be close to 3 and a BCF study for section 5 might be triggered by this value, the requirement for a new log Pow study should be discussed in order to determine a reliable value.	The (other) log Kow of 2.89 was derived by estimation (McFarlane, 2005). However, with the KOWWIN program (v1.67; © 2000 U.S. EPA), a log Pow of 3.5 can be calculated and, moreover, the program's database indicates an experimental log Pow of 2.94 (reference: BioByte, 1995).

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: Remark For the classification and labelling of the preparation the needed classification and labelling of the co-formulants (Risk phrases R65 and R66) should also be considered into account.	
(2)	Vol. 3, B.6.3.2.2, Oral 90-day toxicity (dog) and B.6.3.2.3, Oral 1-year toxicity (dog)	DE: Remark: The liver is clearly the target organ. Therefore, the NOAEL in the 90-day study in dogs is seen at 10 ppm based on concomitant relative liver weight increase and hepatocyte hypertrophy at 200 ppm. Similar effects were noted in the 1-yr study at 400 ppm with the next lower dose of 100 ppm being a clear NOAEL. Thus, 100 ppm (ca 3 mg/kg bw/d) can be considered an overall NOAEL for subchronic toxicity in dogs. Liver effects in dogs should be discussed on an EPCO meeting.	
(3)	Vol. 3, B.6.10.4, AOEL	DE: Proposal: A lower AOEL of 0.03 mg/kg bw/d is proposed that should be derived from the suggested overall NOAEL for subchronic toxicity in dogs (see comment above). Discussion on an EPCO meeting is recommended.	
(4)	Vol. 3, B.6.12, Dermal absorption	DE: Remark: It is not considered appropriate to calculate dermal absorption on a comparison of only urinary excretion following i.v. and dermal administration. Based on the 2nd *in vivo* study (DiDonato and Hazelton, 1991), absorption values of 53% concentrate and up to 36% (dilution) may be assumed but the outcome of the *in vitro* studies that are under way should be awaited.	

section 2 - Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(5)	Vol. 3, B.6.6, Reproduction toxicity (Classification and labelling)	DE: Remark: Myclobutanil caused clear reproductive effects and had an impact on male sex organs in the 2-gen study in rats but these findings were confined to the top dose level of 80 mg/kg bw/d, i.e., a dose in the systemically toxic range. Additional classification and labelling with R62 is not considered necessary and the already allocated risk phrase R63 seems to be more appropriate.	

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)	B.7.3.2 p.7-28	DE: a residue definition should be proposed for myclobutanil	The metabolite RH-9090 was found in rat metabolism along with the parent compound . It cannot be excluded that observed effects (R 63) have been caused by this compound. Moreover acute toxicty (LD50) of R-9090 in mice rwas found in a range of 300-1000 mg/kg (Xn/R22). It is proposed thtat the residue definition of Myclobutanil in food of animal origin should include the metabolite R-9090
(2)	B.7.9 p 7-38; 2nd para	DE: the causality of this conclusion remains unclear	The opposite conclusion results from a DT90 >1 year. Nevertheless a rotational crop study is not deemed necessary since both intended uses are long-lived crops

4. 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, Point 2.6 Effects on non-target species, and Vol. 3, B.9 Ecotoxicology	DE: Myclobutanil belongs to a group of fungicides for which a general concern about a potential for endocrine disrupting effects in humans and wildlife can be stated because of its mechanism of action (triazole fungicides, inhibiting sterol biosynthesis). As myclobutanil in addition shows a rather persistent behaviour this aspect should be included in the risk assessment for the relevant non-target species groups.	There exists also a concern of the EU Commission about a possible endocrine disrupting potential of myclobutanil which is expressed by the classification of myclobutanil as “HPV and/or persistent and/or exposure expected in humans and wildlife, with insufficient data (38 substances)” in the document following of the EU Commission (2004): SEC (2004) 1372 - Commission staff working document on implementation of the community strategy on endocrine disruptors – a range of substances suspected of interfering with the hormone systems of humans and wildlife (COM (1999) 706).
(2)	Vol. 3 B.9.2.13, Residue data in fish	DE: The study indicating a log Pow of 2.56 was actually not accepted by the RMS and should not be mentioned here. Since the log Pow appears to be close to 3 and a BCF study might be triggered by this value, the requirement for a new log Pow study should be discussed in order to determine a reliable value.	The (other) log Pow of 2.89 mentioned in the DAR was derived by estimation (McFarlane, 2005) since the study of Marbot (1993) was not accepted by the RMS due to the method used. However, with the KOWWIN program (v1.67; © 2000 U.S. EPA), a log Pow of 3.5 can be calculated and, moreover, the program’s database indicates an experimental log Pow of 2.94 (reference: BioByte, 1995).
(3)	Vol. 3, B.9.2.16, Exposure and risk assessment for aquatic organisms	DE: The RMS is asked to put out more clearly that risk mitigation measures are needed to show acceptable risks for aquatic organisms when myclobutanil is used in apples.	For use in apples, buffer zones of up to 12 m were needed on FOCUS Step-4 level in order to derive acceptable TER values in the ditch and stream scenarios.

5. 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, level 4, 4.1 identity of the active isomer	UK: The concerns surrounding impurities 3 & 8 are valid since they are present at higher amounts in the technical specification than in the tox batches. The technical specification cannot be modified to reduce the levels as they are seen at these levels in the production control data. Consequently further data on the tox properties of these impurities may be required.	
(2)	Vol 1, level 4, 4.2, physical and chemical properties of the active substance	UK: Spectra for impurity 14 would definitely required prior to Annex I listing if as suggested by the RMS it is deemed to be of toxicological significance	
(3)	Vol 3, B.2.2.19, shelf life at ambient temperature	UK: The storage stability could be dealt with at MS level, but as the notifier plans to submit in the near future it is best to evaluate it as part of the process to produce a more complete package and remove the need for MS's to evaluate data for the representative formulation.	
(4)	Vol 3, B.2.2.29, emulsifiability, stability and re-emulsifiability	UK: Additional emulsion stability data are unlikely to differ from those evaluated already and so are not critical to the Annex I listing of the active substance. As they are being submitted in the near future an evaluation prior to the vote on the listing would be prudent to minimise data gaps.	

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
(5)	Vol 3, B.2.2.29, emulsifiability, stability and re-emulsifiability	UK: Persistent foam can be dealt with on a member state level if required as the differences between the two types of water are unlikely to have significant impact on the level of foam. However we note this is to be included in the shelflife study.	
(6)	Vol 3, B.2.2.32, pourability	UK: The pourability residue is >5%, but has been deemed acceptable by the RMS. Why is this so? Further data on the residue in the sales pack following the rinsing procedure on the label should be requested. This could be addressed at MS level if required.	
(7)	Vol 4, C.1.2.2, identity of isomers, impurities and additives	UK: The RMS has quoted the notifier's statement "no impurities of particular toxicological or environmental concern were observed". Does this cover the potential for the formation of nitrosamines during step 3 of the reaction?	
(8)	Vol 4, C.1.2.4, methods of analysis for the determination of impurities	UK: The precision values from the method validation data for several of the impurities (1-7 & 14) are greater than prescribed in the guidelines. Therefore the method cannot be considered fully validated as stated.	

6. 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.6.2.5, Eye irritation	UK: Classification as eye irritant is not considered appropriate. Vascularisation of the cornea was seen in only 1 out of 9 animals at day 21 in the study of Krzywicki and Bonin, 1984.	
(2)	Vol 3, B.6.10.3, Derivation of the ARfD	UK: The effects observed in the multigeneration study (including increased numbers of stillborn and decreased numbers of females delivering) are considered potentially relevant to acute exposure, and thus the UK considers that the ArfD should be derived using the NOAEL from this study.	With a proposed ARfD of 0.16 mg/kg bw, there is a margin of 200 on the NOAEL for developmental effects. This should give an adequate margin.
(3)	Vol 3, B.6.10.3, Derivation of the AOEL	UK: Due to the magnitude of the liver weight effects in females at 400 ppm in the 1 year dog study, combined with the increased SAP activity and histopathology, the UK considers that this study derives a NOAEL of 100 ppm. This is lower than that obtained in the rat multigeneration study, and should be used in the derivation of the AOEL.	

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
(4)	Vol 3, B.6.12.1, Dermal absorption *in vivo* in rat	UK: In the absence of comparative *in vitro* dermal absorption data, we propose adopting a worst case approach, with dermal absorption values of 50% for the concentrate and dilution.	For the study of DiDonato and Steigerwalt, 1986, the UK considers it more appropriate to derive dermal absorption values based on absorption rather than comparative dermal bioavailability. Therefore, based on levels of radioactivity in urine, funnel wash, faeces and cagewash, dermal absorption values of 26.9% and 44.2% are proposed for the concentrate and dilution respectively. It is noted that levels of radioactivity in the carcass were not determined. The study of DiDonato and Hazelton, 1991, indicates carcass levels of 7.1% for the concentrate and 1.7% for the dilution, giving corrected values of 34% for the concentrate and 45.9% for the dilution respectively. For the study of DiDonato and Hazelton, 1991, based on levels of radioactivity in urine, funnel wash, faeces, cagewash, skin and carcass at 24 hours, with urine levels over 7 days (as while urinary and faecal excretion continues over day 7-14, the increased excretion is comparable to loss of radioactivity from the carcass), dermal absorption values of 53.5% for the concentrate and 29.8% for the dilution are proposed.
(5)	Vol. 3, B.6.15.1, Estimation of operator exposure (Table B.6.15.1-1)	UK: The spray volumes on which the exposure estimates are based (100 – 1200 l/ha for grapevine and 200 – 2000 l/ha for apple) differ from those presented in the GAP table (1000 l/ha for grapevine and 1000 – 1500 l/ha for apple). Similarly, the pack size of 1.5 litres reported in this table differs from the packaging options of 0.25, 0.5, 1, 2, 3 and 5 litre containers described in the DAR.	

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.6.15.1, Estimation of operator exposure (Tables B.6.15.1-2 and B.6.15.1-3)	UK: The German Model estimates for broadcast air-assisted sprayers reported in this table assume a work rate of 15 ha/day and an operator body weight of 60 kg rather than the standard values of 8 ha/day and 70 kg, respectively, in this model.	
(7)	Vol. 3, B.6.15.3, Estimation of bystander exposure	UK: The bystander exposure calculation is based on a spray concentration which differs from that described in the GAP table and also uses data relating to the use of field crop (boom) sprayers (Lloyd and Bell 1983) rather than the equivalent data relating to the use of broadcast air-assisted sprayers (Lloyd *et al* 1987). Also, for assessing the risk to bystanders, a body weight assumption of 60 kg is more appropriate than the value of 70 kg used in this calculation.	
(8)	Vol. 3, B.6.15.4, Estimation of worker exposure	UK: The worker exposure calculation is based on the application rate of 0.048 kg a.s./ha for grapevine and does not consider the higher application rate of 0.090 kg a.s./ha for apple. Also, as the supported uses on grapevine and apple involve a total of 4 applications at 10 day intervals, the assessment should address the likelihood of a build up of foliar residues from multiple applications and the resulting risk to workers.	

7. 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.7.1.3, metabolism, distribution and expression of residues of myclobutanil in wheat	UK: The wheat metabolism study shows a different picture for the fruit crops which may have potential implications for future uses of the Myclobutanil. The presence of small molecular metabolites Triazole Acetic acid and Triazole Alanine is common with other triazole compounds. The RMS's conclusion that formation of these molecules occurs *via.* metabolism in the plant appears valid and is supported by reference to the soil metabolism study.	
(2)	Vol 3, B.7.3.1, residue definition in plants	UK: Agree with tox assessment that RH-9090 should be included in the residue definition as it is potentially significant in apples, and was also observed in the grape metabolism study. The inclusion of RH-9089 would depend upon its toxicity as it was only observed at relatively low levels in the apple and grape metabolism studies (<4%).	
(3)	Vol 3, B.7.3.1, residue definition in plants	UK: If RH-9089 is included in the residue definition then all of the trials would need to be repeated or samples re-analysed for this metabolite. Samples were analysed for parent & RH-9090 and so residue levels should be adjusted in the DAR to be reported as the sum of parent and its metabolite. Subsequent MRL calculations and risk assessments should be repeated taking into account the revised residue levels.	

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.7.11, estimates of potential and actual exposure through diet	UK: Both chronic and acute risk assessments reveal no problems with the proposed MRL's, although this may change depending upon the outcome of the decision on the residue definition and subsequent amendment of the residue levels.	

8. 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.8.2.1, Adsorption and desorption	UK: We note that the adsorption of myclobutanil is postulated to correlate with both CEC and pH. We also note the RMS conclusion that refined PECgw calculations should take this into account. Currently the exposure assessments presented in the DAR appear to be based on the mean Koc value only. Given the relatively narrow range of Koc values, the UK would propose that the use of a mean Koc value is valid and the possible influence of soil pH and CEC does not need to be investigated further.	
(2)	Vol 3, B.8.6.2, Predicted environmental concentration in surface water	UK: As spray drift may be a significant source of surface water contamination for this substance, we would propose that the FOCUS surface water models are also run assuming a single application pattern of the a.s. in case this results in a higher PECsw value compared to the multiple application pattern.	In accordance with the FOCUS surface water guidance, for multiple applications the models should also be run for a single application.

9. Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol 3, B.9.2.16: Exposure and risk assessment for aquatic organisms	UK: It is not explained very clearly why it is necessary to go straight to using FOCUS Steps 3 and 4, or that different buffer zones are applied to different water bodies. It is also noted that the RMS has used 21-day time-weighted average PEC_{SW} for calculation of the chronic fish and aquatic invertebrate TERs. According to SANCO/3268/2001 (Section 3.3) the use of time-weighted average PECs are only appropriate if exposure conditions in the environment are predicted to differ significantly to that in the toxicity studies (taking in to account the fate and behaviour profile of the active substance) and if good information is available on time to onset of effects in the toxicity studies. In the absence of this information, intial PEC values should be used in the chronic assessment and in any case the use of TWA PEC_{sw} has little effect on the outcome of the aquatic risk assessment.	

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.9.2.16, Risk assessment to sediment dwelling organisms	UK: It is noted that the RMS has used 21-day time-weighted average sediment PEC for calculation of sediment dwellers TERs. The spiked water NOEC from the chironomid study has been converted to be a NOEC in sediment (Section B.8.2.9). It is suggested that the sediment dweller TERs should be calculated using a ratio of the spiked water NOEC with the initial surface water PEC. The use of time-weighted average PECs would also need to be fully justified, as discussed above.	
(3)	Vol 3, B.9.5.3: Effects of the formulation on non-target terrestrial arthropods	UK: In the evaluation of the field study conducted with *Typhlodromus pyri*, the RMS concludes that there were no adverse effects on *Typhlodromus pyri* populations following nine applications of 'Systhane 20 EW'. The RMS acknowledges the very low mite population in the untreated control, which remained low for the duration of the study. The UK is concerned that the poor performance of the untreated control may have masked treatment related effects. It is noted that the mite population in the positive control, treated with propineb, were in fact greater than the untreated control on some of the sampling dates. The UK has concerns regarding the reliability of the study and believes the validity of the study should be considered further.	

section 5 - Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(4)	Vol 3, B.9.5.4: Summary of effects, exposure and risk assessment for non-target arthropods	UK: The RMS has concluded that the effects seen on other crop relevant species in tier I studies (e.g. *Coccinella septempunctata*) should be considered further at Member State level; the assessment has not been followed further to higher tier studies. The UK considers that this deficiency in higher tier data/assessment should not be left as a Member State issue. As the potential risk to crop relevant species has not been sufficiently addressed and the fact that the field study with *Typhlodromus pyri* is of questionable validity, it is proposed that the risk to non-target arthropods requires further consideration prior to Annex I listing of myclobutanil.	
(5)	Vol 3, B.9.7: Effects on other soil non-target macro-organisms (and soil organic matter breakdown)	UK: The soil DT90 values for myclobutanil are well in excess of 1 year and (according to Annex point 10.6.2) the need for a litter bag is clearly triggered irrespective of the assessment on collembola. There has been no assessment of effects on OM breakdown using the submitted studies. We note that the mean soil concentrations achieved in the Mallet, 2004 study (up to 0.146 mg a.s./kg soil) are substantially below the peak plateau PECsoil values of 0.359 mg a.s./kg and 0.672 mg a.s./kg determined for vines and apples respectively. The suitability of this study to address the risk to OM breakdown should therefore be discussed.	

10. 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, LOEP, surface tension	NL: The purity of the a.s. from which the surface tension has been measured is only 92.1 %. This is no purified (>98%) material and doesn't meet even the specification for technical a.s. (92.5).	
(2)	Vol. 1, LOEP, AM	NL: Please also indicate the presence of confirmation methods and/or ILV where applicable	
(3)	Vol. 3, B.5.1.2, AM for the determination of significant and/or relevant impurities…….. See also C.1.2.4	NL: It is not allowed to calculate the LOQ. The LOQ is considered to be the lowest level at which acceptable validation data are obtained. The LOQ should be ≤ 0.1% for significant impurities.	
(4)	Vol. 3, B.5.1.2, AM for the determination of significant and/or relevant impurities…….. See also C.1.2.4	NL: Not only the mean recovery data should be given but also the individual data or the range	
(5)	Vol.3, B.5.1.3, AM for the determination of the active substance in ppp	NL: The AM should be fully validated for the 20 EW formulation.	
(6)	Vol.3, B.5.3.1, soil	NL: The source of the soil used for the validation should also be mentioned	

11. 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.6.3.2.2 90-day study dog	NL: The effects on the liver cannot be regarded as 'just' adaptive. The high increase in liver weight (varies from 9%-52%) in combination with the histopathology (centrilobular/midzonal hepatocyte hypertrophy) is definitely an adverse effect. For the females, the NOAEL is 200 ppm (7.88 mg/kg bw/d) and for the males 10 ppm (0.34 mg/kg bw/d).	
(2)	Vol. 3, B.6.3.2.3 1-year study dog	NL: The high increase in liver weight of 27% at 400 ppm in combination with the histopathology (hypertrophy) in 2 animals is an adverse effect. The NOAEL for this study is 100 ppm (3 mg/kg bw/d).	
(3)	Vol. 3, B.6.3.3.3 Percutaneous 28-day toxicity rat	NL: The Material and Methods paragraph is very concise. It is stated that the substance was applied unocclusively to the skin. However, some kind of protection should have been used, otherwise the animals will lick of the substance.	
(4)	Vol. 3, B.6.6 Reproductive toxicity	NL: In the past, myclobutanil was evaluated for a national request for authorisation. In this evaluation, R62 was also proposed and for teratogenicity the proposal was R61.	
(5)	Vol. 3, B.6.10.4 AOEL	NL: If the NOAEL in the dog studies will be reconsidered based on the NL comments (see comments 1 and 2), the 'overall' NOAEL of the dog studies will be 3 mg/kg bw/d. The AOEL will then be 0.03 mg/kg bw/d.	

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section 2 - Mammalian toxicology (B.6)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca. 10 lines)	Column 3 Further explanations
(6)	Vol. 3, B.6.12.1 Dermal absorption (Didonato and Steigerwalt, 1986)	NL: We do not understand the correction for urinary excretion after i.v. exposure. In Table B.6.12.1-2 the recovery after 7 days is reported. The absorbed dose is 28.8% for the concentrate and 47.7% for the dilution, based on the excretion in urine, urine funnel wash, feces, cage wash and ring washes. This is correct. In Table B.6.12.1-4 the absorbed dose is estimated based only on excretion in urine (although in the table it is suggested that also feces was included, but this is not correct). However, the amount excreted in feces should be included! Furthermore, the validity of the i.v. data should be questioned, given the recovery of 124%. Therefore, we propose to use 28.8% and 47.7% for dermal absorption of the concentrate and dilution, respectively.	
(7)	Vol. 3, B.6.15 Exposure data	NL: A NOAEL for local effects after dermal exposure was derived (10 mg/kg bw/d). The external dermal exposure does not exceed this local NOAEL, but this was not evaluated in B.6.15.	

section 3 - Residues (B.7)

12. 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.7.1.1, metabolism in grape	NL: Table B.7.1.1-1: how can the accountability be given when the TRR values were not provided for the different matrices? Were the tabulated values for the unextracted residues calculated values instead of measured values? If there is no reliable data on accountability, is this study then acceptable?	
(2)	Vol. 3, B.7.1.1, metabolism in grape	NL: First study, Nelson, 1984a: is the study with root treatment (growth in treated nutrient solution) representative for the proposed use (spray treatment)?	
(3)	Vol. 3, B.7.1.2, metabolism in apple	NL: Table B.7.1.2-1: (1) The TRR in the methanol extract of the pomace is missing from this table. (2) Were the unextractable residues not determined?	
(4)	Vol. 3, B.7.1.2, metabolism in apple	NL: The extractability figures for pomace in the text may not be correct (based on radioactivity level in chloroform extract, but should be based on radioactivity level in methanol extracts).	
(5)	Vol. 3, B.7.1.3, metabolism in wheat	NL: Table B.7.1.3-1: how can the accountability be given when the TRR values were not provided for the different matrices? Were the tabulated values for the unextracted residues calculated values instead of measured values? If there is no reliable data on accountability, is this study then acceptable?	

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section 3 - Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(6)	Vol. 3, B.7.1.3, metabolism in wheat	NL: Table B.7.1.3-1: The TRR in the methanol extracts is missing from this table.	
(7)	Vol. 3, B.7.2.1, metabolism in lactating cow	NL: Test substances: why is the value for logPow given? To which compound does the value of 2.55 pertain?	
(8)	Vol. 3, B.7.2.1, metabolism in lactating cow	NL: In the study conclusion it is stated that myclobutanil was extensively oxidised into RH-9090, and that RH-9090 was further oxidised into RH-9089. Since however the cows were dosed with a mixture of 14C radiolabeled parent compound, 14C-RH-9090 and 14C-RH9089, in a ratio of 32:58:10, which evidence is there that RH-9090 and RH-9089 are indeed degradation products formed in the lactating cow?	
(9)	Vol. 3, B.7.2.2, metabolism in laying hens	NL: Table 7.2.2-3 and text below table: what is meant by “Undissociated lactone/RH-9090/RH-9089”?	
(10)	Vol. 3, B.7.2.3, metabolism in pigs	NL: Appendix A, metabolic pathway in plants and animals: Figure 3, the drawn structure of M2 (isomer) (metabolite in rat) is unclear. Is the structure identical to 4-hydroxy-3-lactone found in cow and hen?	
(11)	Vol. 3, B.7.1-B.7.3	NL: At several places it is stated that RH-9090 (alcohol) is reduced to RH-9089 (ketone). This step is an oxidation, not a reduction.	

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
(12)	Vol. 3, B.7.3.1, residue definition plants	NL: Based on the metabolism studies, a conversion factor may be proposed to include the metabolite RH-9090 in the residue definition for risk assessment (7-9% TRR free and 5-6% TRR as glucoside in grape; 11.5% TRR free and 20.9-23.4% TRR as glucoside in apple). Is the non-inclusion based on the results of the field residue trials?	
(13)	Vol. 3, B.7.3.2, residue definition animal products	NL: See comment 8: which evidence is there that RH-9090 and RH-9089 are indeed degradation products formed in the lactating cow?	
(14)	Vol. 3, B.7.3.2, residue definition animal products	NL: Last paragraph: in the metabolism study at the 1X dose level, total radioactive residues in liver and milk were >0.01 mg/kg (0.11 and 0.029 mg eq./kg respectively).	
(15)	Vol. 3, B.7.6.1, residues in supervised trials	NL: Several trials in apples with a spray concentration of 0.0045 kg a.s./hL were not accepted as the dose in terms of kg a.s./ha was <25% below the cGAP rate of 0.09 kg a.s./ha. However, the spray concentration was within 25% of that of cGAP (0.006 kg a.s./hl), and the trees were spayed to run-off. Are these trials not acceptable, since the key parameter determining the residue when orchards are sprayed is not the areal dose, but the spray concentration?	

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
(16)	Vol. 3, B.7.6.1, residues in supervised trials	NL: Certain trials in grape used a spray concentration of 0.003 kg a.s./hL, which is >25% below that of cGAP (0.0048 kg a.s./hL), but these trials were accepted since the the dose in terms of kg a.s./ha was within 25% of that of cGAP. Is the key parameter determining the residue when orchards are sprayed not the spray concentration instead of the areal dose?	
(17)	Vol. 3, B.7.6.1, residues in supervised trials	NL: Several trials in grape with a spray concentration within 25% of that of cGAP were not accepted as the dose in terms of kg a.s./ha was <25% below the cGAP rate of 0.048 kg a.s./ha. Are these trials not acceptable, since the key parameter determining the residue when orchards are sprayed is not the areal dose, but the spray concentration (when sprayed to run-off)?	
(18)	Vol. 3, B.7.7.1, effect on nature of residues	NL: The conditions for hydrolysis described in Annex I of appendix E of the Lundehn document (90-120°C) are more severe than in the available hydrolysis study (50°C). The data on heat stability of pure myclobutanil obtained during boiling point determination are not relevant to address hydrolytic stability. Hydrolysis studies are required, performed according to the procedures in Annex I of appendix E of the Lundehn document.	

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
(19)	Vol. 3, B.7.7.2, effect on magnitude of residues	NL: Transfer factors for wet apple pomace were 0.55 and 0.646 in the first two trials, but much higher (2.87 and 2.97) in the last two trials. How can the difference be explained? Why is it stated under "Conclusion" that the average transfer factor for wet apple pomace is 2.97? Are the results from the first two trials not valid?	
(20)	Vol. 3, B.7.8, livestock feeding studies	NL: The intake for livestock is based on the maximum residue in wet apple pomace in the two processing trials at cGAP. However, is it not more appropriate to correct the highest residue, measured in apple fruit in all acceptable trials, by the average transfer factor for apple pomace? That would give a much higher value, based on residues data in apples from far more trials than two.	
(21)	Vol. 3, B.7.9, rotational crop studies	NL: It is stated that studies on residues in rotational crops are not required based on the DT90 (field) and (lab) values ((>1 year and 637-1906 days respectively). These DT90 values however would trigger studies on residues in rotational crops.	
(22)	Vol. 3, B.7.11.2, NESTI calculations	NL: Details on the calculations of STMR-P for all processed products would be helpful for transparency.	

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
(23)	Vol. 3, B.7.14, storage stability	NL: Results for 24 months for almond hulls (parent + metabolite) are not acceptable since the residues were corrected for procedural recoveries which were <70%. This applies also to almond meat, metabolite only, after 24 months. It is considered to be more appropriate to assign a storage stability of 18 months in these cases.	
(24)	Vol. 1, 2.4.1, definition of residues relevant to MRLs	NL: Which evidence is there that RH-9090 and RH-9089 are indeed degradation products formed in the lactating cow (see also comment 8 and 13)?	
(25)	Vol. 1, 2.4.1, definition of residues relevant to MRLs	NL: Revised intake calculations for livestock (see comment 20) might lead to a higher intake and necessitate comparison with higher dose groups from the feeding study.	
(26)	Vol. 1, List of Endpoints, storage stability	NL: Data from other commodities (almond, cucumber, tomato) may also be included.	
(27)	Vol. 1, List of Endpoints, critical residues data	NL: The STMRs for apple and grape are apparently based on the combined data set from Europe-N and Europe-S. The STMRs for the separate regions (vol. 3, B.7.6.1) are higher than the values in the Endpoints. Is it justified to combine the data from the N and S regions? In particular for grape the data sets seem to differ substantially.	
(28)	Vol. 1, List of Endpoints, processing factors	NL: For apples transfer factors from all 4 trials for e.g. wet pomace were included, but in vol. 3, B.7.7.2, the conclusion only referred to the transfer factors from two studies (see also comment 19). How can this discrepancy be removed?	

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

13. 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, Level 2, 2.1.4. , Classification and Labelling, Table 2.1.4-1	NL: The environmental safety phrases S60 and S61 are assigned to formulated products and not to the active substances	
(2)	Vol.1, Level 2, 2.5.3 Fate and behaviour in water, Impact on water treatment procedures	NL: The active substance is myclobutanil in stead of the metconazole mentioned here.	
(3)	Vol. 3, B.8.4.1 Hydrolysis rate of relevant metabolites , degradation and reaction products	NL: The information in the table on page 8-22 is correct, but the format is rather unusual.	

14. 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, Subchronic and reproductive toxicity to birds	NL: Albinism was observed, which might reduce life expectancy in the field. From the summary it is not clear in which group(s) this occurred and if it has a connection with the dose rate.	
(2)	Vol. 3, B.9.1.8 Risk assessment for birds and B.9.3 Idem for mammals	NL: If the risk of consumption of drinking water should only be assessed for leafy crops, this should be put down in an EFSA agreement list.	
(3)	Vol. 3, B.9.2.11 Acute toxicity of the preparations	NL: It would be good to also express the endpoints as mg a.s./L, and to include both in the LoE (mg form./L as well as mg a.s./L).	
(4)	Vol.3, B.9.5.1 Effects on non-target arthropods	NL: Relevant endpoint for risk assessment is corrected mortality (and effect on reproduction), not reduction of beneficial capacity, according to ESCORT 2. Preferably L(E)R50's are calculated.	
(5)	Vol. 3, B.9.5.1, Semi-field bioassay with *A. rhopalosiphi*	NL: Methods used are not very clear. Were only hop plants sprayed, or both hop and barley plants? Were effects only tested for after the 4rd spraying?	
(6)	Vol.3, B.9.5.4 Risk assessment for non-target arthropods	NL: Pardosa is not mentioned in the risk assessment, although a study is available. IOBC classifications are generally not used anymore.	
(7)	Vol.1, LoE, NTA	NL: It might be helpful to describe the semi-field and field study in more detail (crop, country etc) in the LoE.	
(8)	Vol.3, B.9.6.6, First tier risk assessment of the formulation Systhane 24E	NL: Is this formulation comparable to Systhane 20EW?	

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section 5 - Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(9)	Vol.3, B.9.7, Effects on other soil non-target macro-organisms	NL: In the risk assessment, nothing is said about the litterbag study.	
(10)	Vol.1, LoE	NL: Why are the litterbag study, studies on non-target plants and sewage treatment not included in the LoE?	
(11)	Vol.3, B.9.8.4 Risk assessment for soil micro-organisms	NL: Results of the studies should be compared to the PECs before concluding that the risk is acceptable.	
(12)	Vol. 3, B.9.10 Effects on sewage treatment	NL: It is not clear how the risk assessment is performed (it is only concluded that the risk is acceptable).	

15. Physical/Chemical Properties; Detail 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)	Column 3 Further explanations
(1)	Vol. 1, Level 1, 1.3.1 Name and address of applicant, pg 5 Vol. 3, B.1.1.1, pg 1-2	DAS: please change the Central address and contact person Dow AgroSciences, European Development Center 2nd Floor Milton Park Abingdon OX14RN – OXON United Kingdom [redacted] Regulatory Team Leader, Europe Phone ++39 02 48224086 Fax ++29 02 48224384	
(2)	Vol. 1, Level 1, 1.4.2 Manufacturer of the plant protection product, pg 8 Vol. 3, B.1.2.2, pg 1-5	DAS: please change Dow AgroSciences B.V. to Dow AgroSciences Italia S.r.l	
(3)	Vol. 1; 2.1.1 Identity, pg 16 Vol. 1, Level 4, 4.1 Identity of the active substance, Impurity profile, pg 76 *"The notifier should provide a case and/or data to show that the increased levels of both impurities will not have a significant adverse effect on the toxicity of technical Myclobutanil."*	DAS: a position document for the impurities in myclobutanil batch, including an assessment on the QSAR analysis was provided to RMS (June, 2005). QSAR assessment: DEREK reported no alerts. TOPKAT noted skin sensitisation and ocular irritation for both impurities at different severity levels (**imp. 3** being more severe), though accuracy cannot be determined. DEREK included skin sensitisation/ocular irritancy endpoints.	It is the opinion of the Notifier that further toxicological testing with the new source (or even the impurities themselves) is not required, and would not add value to the assessment already carried out. Following the principles of the "Guidance Document on the Assessment of the Equivalence of Technical Materials of Substances Regulated Under Council Directive 91/414/EEC", the situation is the following:

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<table>
<tr><th>No.</th><th>Column 1
Reference to Draft Assessment Report</th><th>Column 2
Comment (restricted to 500 characters)</th><th>Column 3
Further explanations</th></tr>
<tr><td></td><td></td><td>Excedance of imp. 3 (with greater predicted severity level) above the acceptable maximum limits (8% or 1g/kg) would not cause concern for these 2 tox end-points with new source.
TOPKAT assessment of imp. 8 shows lower severity levels for eye irritation/sensitisation, though sensitivity of this prediction is not clear. However, based on available data, the increased levels of this impurity in the new source would not lead to a change in hazard potential for myclobutanil.</td><td>Impurity levels and acceptable increases
<table><tr><th>Impurity (non-relevant)</th><th>Reference Batches (used in tox studies) = certified limit</th><th>5-Batch, spec.</th><th>Latest batch (permitted max level)</th></tr><tr><td>Imp. 8</td><td>1-3 g/kg

(i.e. ≤6 g/kg)</td><td>3 g/kg</td><td>9 g/kg (6g/kg; twice acceptable max increase)</td></tr><tr><td>Imp. 3</td><td>8-12 g/kg

(i.e. >6 g/kg)</td><td>8-11 g/kg</td><td>19 g/kg (18 g/kg; 8% more than acceptable max increase)</td></tr></table>
Imp. 3: tested in in vitro Ames test - negative for mutagenicity. Batch also used in the rat/mouse carcinogenicity and rabbit developmental toxicity studies. The increased level of this impurity in the manufactured batch is not toxicologically significant. This impurity (at these levels) would need to be very potent to cause the degree of toxicity observed in these studies with myclobutanil. Therefore, increase to 19 g/kg is considered acceptable and of no toxicological concern.

Imp. 8: tested in in vitro Ames test, chromosome aberration test, UDS assay, mouse in vivo chromosome aberration test, and dominant lethal test - negative for all end-points. At least one of these batches was also tested in the acute toxicity, 28-day dog toxicity, rat 2-generation and</td></tr>
</table>

<table>
<tr><th>No.</th><th>Column 1
Reference to Draft Assessment Report</th><th>Column 2
Comment (restricted to 500 characters)</th><th>Column 3
Further explanations</th></tr>
<tr><td></td><td></td><td></td><td>developmental toxicity and rat carcinogenicity studies. Therefore, there is a comprehensive database on the reference material containing up to 3 g/kg Imp. 8. This impurity would need to be very potent in order for the 6g/kg increase to result in toxicity more severe than that caused by myclobutanil. Based on these data, increases to 9 g/kg is considered acceptable and of no toxicological concern.

Myclobutanil is an eye irritant but not a skin sensitizer, and already currently carries classification/labeling for this effect.
<table>
<tr><th>Test on active</th><th>Ref. Lot no.</th><th>Imp 3 g/kg</th><th>Imp 8 g/kg</th><th>Result</th></tr>
<tr><td rowspan="2">Eye irritation</td><td>83159-5</td><td>8</td><td>3</td><td>Eye irritant R36</td></tr>
<tr><td>LSPL 83-0017E</td><td>10</td><td>3</td><td>Non-irritant</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>M&K</td><td>83159-7</td><td>9</td><td>3</td><td>Non-sensitiser</td></tr>
</table>
Increased levels of these impurities should not affect these test results to change the hazard assessment of myclobutanil.</td></tr>
<tr><td>(4)</td><td>Vol. 1; 2.1.2 Physical and chemical properties, pg 16
Vol. 3, B.2.2.19, pg 2-17</td><td>DAS: the shelf-life study is on going, the final report will be submitted by October 2006.</td><td></td></tr>
</table>

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

No.	Column 1 Reference to Draft Assessment Report	Column 2 Comment (restricted to 500 characters)	Column 3 Further explanations
(5)	Vol. 1, 2.2.1 Analytical Methods for analysis of active substance, pg. 19 *"for relevant impurity 14 the proposed LOQ of 0.036% remains to be validated.."* Vol. 1, List of end points, Impurities in technical as, pg 44 Vol. 1, Level 4, 4.5 Methods of analysis, pg 76 Vol. 3 B.5.1.2 Method for impurities, Conclusions, pg 5-4	DAS: the validation report for impurity 14 was sent to the RMS (August, 2005). Results for precision/recovery were acceptable. Testing at the level of 0.036% impurity 14, resulted in an acceptable recovery of 89% and acceptable precision by utilizing the horwitz equation.	
(6)	Vol. 1, 2.2.3 Analytical Method - Air, pg 19 Vol. 1, List of end points, Analytical methods for residues, Air, pg 44 "*additional validation data required*" Vol. 1, Level 4, 4.5 Methods of analysis, pg 76 Vol. 3 B.5.5.3 Analytical methods (residue) for soil, water and air, Air pg 5-16	DAS: A new method, "Method Validation Study for the Determination of Myclobutanil in Air" was developed in 2005 to replace the original method outlined in the dossier and was sent to the RMS (August, 2005).	The new analytical method was developed and validated for the determination of myclobutanil in air with a limit of quantification (LOQ) of 0.7 µg/m^3 and limit of detection (LOD) was approximately 0.05 µg/m^3. Specificity was ensured by the use of LC/MS/MS with two MRMs. The new method fulfills registration requirements specified in the Council Directive 91/414/EEC Annex II (Part A, Section 4.2.4), as amended by Commission Directive 96/46/EC and detailed in the EC Guidance documents on residue analytical methods (SANCO/825/00 rev. 7, 17/03/04 and SANCO/3029/99 rev. 4, 11/07/00).

No.	Column 1 Reference to Draft Assessment Report	Column 2 Comment (restricted to 500 characters)	Column 3 Further explanations
(7)	Vol. 1, Level 4, 4.2 Physical and chemical properties of the as, Spectra of impurities, pg 76 *"Notifier should provide spectra of relevant impurity 14"* Vol. 3 B.2.1.10, pg 2-5	DAS A spectra report was submitted to the RMS (August, 2005). The mass spectrum, carbon and proton NMR spectra and the IR spectrum of impurity 14 were consistent with the structure. The UV/Vis spectra were obtained in acidic, neutral, and basic media; wavelength maxima, band widths and extinction coefficients were calculated. The water content of the sample was found to be 0.3% using Karl Fischer coulometric titration.	
(8)	Vol. 3 B.5.1.3 Method for myclobutanil in Systhane 20EW, pg 5-4 / 5-5 *Method TM 96-176-02 (GC-FID on DB-1, internal standard octacosane in ethyl acetate), which was the basis for method DAS-AM-04-042, has been used in the storage stability studies with Systhane 20EW. Validation report for this method was not available for submission.*	DAS: a justification was submitted to the RMS (June, 2005): within the validated method DAS-AM-04-042 for Systhane 24EC pentadecane was used as the internal standard. When pentadecane was used with Systhane 20 EW it became an interference issue and octacosane was used in its place. Octacosane was analyzed using the conditions from DAS-AM-04-042 and compared with Systhane 20 EW and no interferences were observed. The linearity within DAS-AM-04-042 also bracketed the proper range for Systhane 20 EW. Therefore DAS-AM-04-042 can be used as a validated method for Systhane 20 EW only using octacosane instead of pentadecane as the internal standard. The available Chromatograms of Systhane 20 EW formulation blank, a myclobutanil technical, and an internal standard of octacosane show no interferences and were analyzed using the gas chromatographic conditions within DAS-AM-04-042	

16. Mammalian Toxicology (B.6)

<table>
<tr><th>No.</th><th>Column 1
Reference to Draft Assessment Report</th><th>Column 2
Comment (restricted to 500 characters)</th><th>Column 3
Further explanations</th></tr>
<tr><td>(1)</td><td>Vol. 1, 2.3.1 Classification and Labeling, Table 2.3.1-1 Summary of acute toxicity of myclobutanil pg 20-21 – Classification

Vol. 3 B.6.2.7 Summary of Acute toxicity, pg 6-17</td><td>DAS: Based on a requirement of the Brazilian Authorities, a new package of acute toxicity studies have recently been conducted with myclobutanil technical grade from the actual registered source.
A summary of the new data are presented below. Based on these data using current test guidelines, myclobutanil should not be classified for acute toxicity. Therefore, the proposed classification for myclobutanil should be amended to reflect the new data generated.
<table>
<tr><th>Route/ method</th><th>Species/ strain (sex)</th><th>Result</th><th>EC class.</th><th>Ref.</th></tr>
<tr><td>Oral/gavage/ Up-Down Method</td><td>Rat/F344 (F)</td><td>LD_{50} = 3129 mg/kg bw/day</td><td>Non e</td><td>Moore, 2005</td></tr>
<tr><td>Dermal/topic al</td><td>Rat/F344 (M/F)</td><td>LD_{50} = > 5000 mg/kg bw/day</td><td>Non e</td><td>Moore, 2005</td></tr>
<tr><td>Dermal/topic al</td><td>Rabbit/NZ W (M/F)</td><td>Slight irritation</td><td>Non e</td><td>Moore, 2005</td></tr>
<tr><td>Eye/instillatio n</td><td>Rabbit/NZ W (M)</td><td>Mild irritation</td><td>Non e</td><td>Merkel 2005</td></tr>
<tr><td>Dermal/LLNA</td><td>Mouse/ Balb C (F)</td><td>Non-sensitiser</td><td>Non e</td><td>Woolhi ser.20 05</td></tr>
</table></td><td>In the Fischer 344 rat, myclobutanil is of low acute oral and dermal toxicity with the LD_{50} at 3129 mg/kg bw/day and >5000 mg/kg bw/day, respectively. Myclobutanil, in rabbits, was slightly irritating to skin and a mild eye irritant (Table below), but no effects were seen from 72 hours after application. Myclobutanil is not a skin sensitiser in the mouse (LLNA).

Summary of data from eye irritation study: Mean values for ocular lesions 24, 48 and 72 hours after instillation
<table>
<tr><th rowspan="2">Animals</th><th rowspan="2">Corneal opacity</th><th rowspan="2">Iridial lesions</th><th colspan="2">Conjunctival</th></tr>
<tr><th>Redness</th><th>Chemosis</th></tr>
<tr><td>1</td><td>0.33</td><td>0.33</td><td>1</td><td>0.33</td></tr>
<tr><td>2</td><td>0</td><td>0.33</td><td>1</td><td>0.33</td></tr>
<tr><td>3</td><td>0.33</td><td>0.33</td><td>1</td><td>0.33</td></tr>
<tr><td>EC trigger values*: (R36)</td><td>≥ 2.0, < 3</td><td>≥ 1.0, < 2.0</td><td>≥ 2.5</td><td>≥ 2.0</td></tr>
</table>
*Classification triggered if any EC value is attained by two or more animals</td></tr>
</table>

No.	Column 1 Reference to Draft Assessment Report	Column 2 Comment (restricted to 500 characters)	Column 3 Further explanations
(2)	Vol. 1, 2.3.1 Reproductive toxicity and teratogenicity, Proposal for R62, pg 25 Vol. 1, List of end points Impact on Human and Animal Health, Reproductive Toxicity pg 61-62 Vol. 3, B.4.1, Table B.4.1-1, pg 4-2 Vol. 3, B.6.6.1.1 Two generation reproductive toxicity in the rat Conclusion, pg 6-53 Vol. 3, B.6.6.3 Summary of reproductive toxicity and teratogenicity, pg 6-58	DAS: There is no clear evidence that the testicular atrophy observed only in aged rats (first noted at 12 months in the 2-year rat carcinogenicity study) and P2 males (following 27 weeks exposure in the 2-generation reproduction study) caused impaired fertility. Effects observed in the top dose group of the 2-generation study included reduction in the number of viable foetuses and numbers of females delivering, and an increased number of pups born dead. These effects are most likely the result of post-implantation loss and/or perinatal death, rather than a consequence of impaired fertility. This information would suggest that the effects observed in the 2-generation study were due to developmental toxicity and not impaired fertility. The relevance to humans of this species-specific testicular atrophy remains unclear and R62 classification is unwarranted.	In summary, testicular atrophy (and associated sequelae) were observed only in the male rat at systemically toxic doses, but not in any other species studied (mouse 2-year carcinogenicity study and dog 1-year toxicity study) at comparable doses. In addition, this finding was present only in the 2-year carcinogenicity study and the second generation of the 2-generation reproduction toxicity study, but not in any shorter term rat studies. It should be noted that testicular atrophy is a common finding in the ageing rat. The decrease in the number of mated females which delivered in the P2/F2a mating, was similarly seen for the P1/F1a mating, and therefore cannot be directly attributed to the testicular effects in the P2 males. Furthermore, changes in fertility were not noted in a dominant lethal study in which a single gavage dose of 0, 10, 100 or 735 mg/kg bw myclobutanil did not result in a dominant lethal effect through 8 weeks of mating. Dominant lethal studies are designed to detect effects on pregnancy rates, live foetuses/litter, total implants and foetal deaths. There was no indication of a dosage-dependent increase in foetal death, even at an adult-lethal dosage. Also, the rat (and rabbit) developmental toxicity study clearly demonstrated embryo/foetotoxicity with reduced viability index, and increased number of resorptions at oral gavage doses of 93.8 mg/kg bw/day or higher. If these dams in the developmental study had been allowed to deliver their litters, a similar pregnancy outcome may have occurred as that observed with the 2-generation study. Although the dose levels cannot be directly compared due to the difference in dose-rate in the two studies (i.e., bolus effect in gavage studies vs. slower rate of intake in the diet study), the effects are qualitatively consistent. In the 2-year carcinogenicity study, the incidence of bilateral testicular atrophy was increased at 39.2 mg/kg bw/day and the effect appeared to be progressive with time and dose. This was first noted at the 12-month time-point.

No.	Column 1 Reference to Draft Assessment Report	Column 2 Comment (restricted to 500 characters)	Column 3 Further explanations
			The incidence of unilateral testicular atrophy was comparable to controls at each time-point. The gross pathology findings of reduced testis size did not directly correlate with the histopathological findings. Testes weights were decreased (12-25% at the top dose) with increasing time. Microscopically, the seminiferous tubules were frequently devoid of spermatid formation and germinal epithelial cells. In severe cases, only Sertoli cells remained. These findings account for the gross appearance of atrophy. The testicular effects in the control and low dose (2.5 mg/kg bw/day) were comparable, and no abnormalities were seen at 3 and 6 month time-points at any dose level. The incidences of other findings in the testes, such as polyarteritis, did not show the same pattern of dose or time relationship. It should be noted that atrophy was not observed histopathologically at 106 mg/kg bw/day in the MTD 2-year rat carcinogenicity study, though aspermatogenesis and hypospermia were seen.In the 2-generation reproductive toxicology study, similar testicular effects were observed in the second generation adult males, but not in the P1 generation males. The changes were primarily increased incidence of diffuse testicular atrophy, prostatic atrophy, necrotic spermatocytes/spermatids and decreased spermatozoa in the epididymides. This pattern correlates with the more pronounced evidence of systemic toxicity in P2 animals relative to the P1 animals. For example, histologic changes in the liver were seen in the middle-dose P2 males, but not in P1 males at 16 mg/kg bw/day. Reduced weight gain was also seen in P2, but not P1, 80 mg/kg bw/day males. *Impact on fertility.* A total of four matings (two litters per generation) were performed in the study, thus providing ample data to assess fertility. Consistent with the lack of histopathological changes in the male reproductive organs, there was no convincing evidence of an effect on fertility in the F1 generation. Although the number of F1a high-dose females giving

No.	Column 1 Reference to Draft Assessment Report	Column 2 Comment (restricted to 500 characters)	Column 3 Further explanations
			birth (20) was slightly lower than control (23), this was not repeated in the F1b litter. In fact, the number of high-dose females giving birth following the F1b mating (23) was slightly higher than that of controls (22). Regarding male fertility, individual animal data in the study report were used to calculate the number of males which successfully sired a litter of viable pups. It was found that 25/25 (100%) of the high-dose group P1 males were fertile vs. 24/25 (96%) in the control P1 males. These data clearly indicate that there were no adverse effects on fertility among the P1 males and females. The two matings of the P2 adult animals revealed a decrease in the number of high-dose group females giving birth relative to controls. Again, male fertility indices were not provided in the study report, but were calculated based on individual animal data shown in the report appendices. The percentage of high-dose P2 males which successfully sired a litter (18/25, 72%) was decreased relative to controls (24/25, 96%). Interestingly, there was a very close individual animal correlation between histopathological changes in the testes and epididymides, and the failure of males to sire a litter. Six of the seven high-dose males that failed to sire a litter exhibited these histopathological changes at necropsy. This might suggest that the failure to sire a litter was secondary to the testicular atrophy and associated histopathological changes. *Litter data.* At 80 mg/kg bw/day, the number of pups born dead was increased in all four matings. However, this appeared to be a marginal effect, as the percentage of pups born alive was no lower than 94.7%, vs. a low of 98.6% among the controls. The incidence of dead pups was not markedly different between the first and second generations. The total number of pups per litter (i.e., includes live and dead pups) was not affected by treatment in either the F1a or F1b matings. In the F2a and F2b matings, total number of pups per litter was statistically decreased at the high dose level of 80 mg/kg bw/day. However, the number of pups per litter in the high-dose F2b litter (13.4) was similar to the number

No.	Column 1 Reference to Draft Assessment Report	Column 2 Comment (restricted to 500 characters)	Column 3 Further explanations
			in the F2a controls (13.8), again suggesting that this effect was marginal. There was no increase in pup mortality from postnatal day 4 onward, although pup body weights were decreased in the high dose group in all matings.
(3)	Vol. 1, 2.3.1 Reproductive toxicity and	DAS: as agreed with the RMS, the notifier reviewed the	The skeletal tissues have been re-examined by Dow

No.	Column 1 Reference to Draft Assessment Report	Column 2 Comment (restricted to 500 characters)	Column 3 Further explanations
	teratogenicity, skeletal observations: 7th cervical ribs, pg 26 *"More information from the Company could clarify this point"* Vol. 1, List of end points Impact on Human and Animal Health, Reproductive Toxicity pg 61-62 Vol. 3, B.6.6.2.1 Teratogenicity test by the oral route in the rat Foetal morphological observations; Conclusion, pg 6-55 Vol. 3, B.6.6.3 Summary of reproductive toxicity and teratogenicity, pg 6-58	available data and issued the report "Re-analysis of selected skeletal findings from a teratology study with RH-53,866 (myclobutanil) in Rats" that was sent to the RMS (December, 2005). Re-evaluation of the skeletal specimens showed a small, biologically significant (not statistically) increase in incidence of 7th cervical ribs at a high dose (469 mg/kg bw/day) only. Total incidence of 4 foetuses in 3 litters is minimal, occurring at a maternally toxic dose, which also showed a significant increase in resorbed implantations and reduced viability. Incidences of 14th rudimentary rib were also only increased in this high dose group, affecting a total of 6 foetuses in 6 litters (litter effect statistically significant). Given marginal nature of these supernumerary rib increases, lack of any corresponding pattern of fetal malformation, and presence of maternal toxicity during the critical period for supernumerary rib induction, these skeletal alterations represent foetotoxicity, <u>not</u> teratogenicity, associated with maternal toxicity. This finding itself does not warrant classification, and should not be included in the R63 definition for myclobutanil.	Chemical to assess the incidences of 7th cervical ribs and 14th rudimentary ribs in all of the foetuses in accordance with current practice. Re-evaluation of the skeletal specimens using length criteria similar to that recommended in several recent publications showed a complete lack of true 7th cervical or 14th rudimentary ribs at dose levels of 31.3, 93.8 and 312.6 mg/kg/day. In the high dose group, the incidences of both skeletal alterations were just slightly above expected control incidences based on published data using similar rib length criteria and, therefore, were considered to be treatment-related effects. Foetuses are susceptible to such effects. Notably, significant skeletal alterations were not observed in the rabbit.
(4)	Vol. 1, 2.3.1 Toxicity studies on metabolites and supplementary studies, pg 27 and Table 2.3.1-7 pg 28 Triazolylalanine (TA), *"…classification for developmental effect as cat. 3 R63 is therefore proposed."*	<u>DAS:</u> TA is not a toxicologically relevant metabolite and thus would not be classified in category 3 (R63). *"Developmental toxicity of TA (Clapp et al., 1983)"*, assessed according to regulatory guidelines, showed a number of skeletal variations in foetuses at the highest dose level at higher incidence than in controls on a <u>foetal</u> basis. The findings occurred in the absence of maternal toxicity. A relationship to treatment is possible, but findings are considered to be of no	<u>Summary of position of the TDMG</u> **(Triazole Derived Metabolite Group**) Classification and labelling guidance states: "*In general, classification in Category 3 or no category would be assigned on an ad hoc basis where the only effects recorded are small changes in the incidences of spontaneous defects, small changes in the proportions of common variants such as are observed in skeletal examinations, or small differences in postnatal developmental assessments."* These findings (odontoid and 5th sternebra not ossified, 13th thoracic

***** 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.

No.	Column 1 Reference to Draft Assessment Report	Column 2 Comment (restricted to 500 characters)	Column 3 Further explanations
	Vol. 3, B.6.8.1.2 Triazolylalanine Developmental rat study, conclusions, pg 6-69 Vol. 3, B.6.8.3, Summary of Toxicity studies, pg 6-71	biological significance, not to be adverse and represent typical aspects of normal development because: • The low number of changes involved (including both more and less ossification) • The lack of impact on the foetus, given the changes are part of normal development • The increased incidences of isolated skeletal variations are seen at high dose levels only There is no evidence for a concommitant effect (i.e. decrease) on pup weight	centrum, 4th lumbar transverse process and 7th cervical transverse process partially ossified (bilateral)) occurred in the absence of maternal toxicity. A relationship to treatment is possible, but findings are considered to be of no biological significance, not to be adverse and represent typical aspects of normal development for the following reasons: • **The low number of changes involved (including both more and less ossification):** Whilst statistical differences exist for this small number of findings, they are few in comparison with the total number of skeletal structures evaluated, they are isolated findings in different unrelated locations within the foetal skeleton and all represent aspects of normal development. Partial ossification of the 4th lumbar and 7th cervical transverse processes actually represent more and not less ossification for this stage of development, whereas the other structures are less ossified. It is highly unlikely that more progresses and retarded ossification of skeletal structures is induced simultaneously by the test substance. Thus, this lack of a consistent effect on ossification is indicative of normal variation, not retarded development, with no indication that an impaired process of ossification prevents normal completion. • **The lack of impact on the foetus, given the changes are part of normal development:** The skeletal centres of interest are particularly labile at this stage of gestation as the process of ossification progresses through prenatal to postnatal development. If the process of ossification had been impaired by treatment, it would be reasonable to expect that the skeletal structures in the same location would also have been affected. This is not the case. For example, for evidence of retarded ossification, an increased incidence of non-ossification of the cervical centra would be expected in addition to non-ossification of the odontoid; an increased incidence of partial ossification of other thoracic centra (10th-12th in particular, as they also tend to be labile at this time) would be expected in addition to partial ossification of the 13th centrum; an increased incidence of partial ossification of the 2nd, 5th or 6th sternebrae would be expected in addition to non-ossification of the 5th sternebra. Other areas of the skeleton would also be affected, e.g. the skull, *manus* and *pes*. The skeletal centres showing

No.	Column 1 Reference to Draft Assessment Report	Column 2 Comment (restricted to 500 characters)	Column 3 Further explanations
			statistically significant differences are isolated and not part of a continuum of change due to treatment. • **The increased incidences of isolated skeletal variations are seen at high dose levels only:** The statistically significantly increased incidences were seen only at the 1000mg/kg dose level when analysed on a foetal basis (except for odontoid not ossified, which was also statistically significantly increased at 300mg/kg). However, recent reanalysis of the data on a litter basis (appropriate unit of comparison for developmental toxicity) removes the statistical significance of the change at 300mg/kg and the finding at the top dose for 5th sternabrae. Therefore, NOEL for this study, 100mg/kg, is a conservative estimate. • **There is no evidence for a concommitant effect (i.e. decrease) on pup weight:** This is often seen when pup development is retarded/delayed.
(5)	Vol. 1, 2.3.1 Toxicity studies on metabolites and supplementary studies, pg 29 Triazolylalanine (TA), "*triazolylalanine should be considered as relevant metabolite from a toxicological point of view…*" Vol. 1,List of end points Impact on Human and Animal Health, Other toxicological studies Triazolylalanine (TA),pg 62	DAS: We do not consider TA to be a relevant metabolite of myclobutanil as its toxicity is significantly lower than the active substance itself. It is agreed that the conservative NOEL for developmental toxicity effects is 100 mg/kg bw/day. This is higher than the NOAEL (31 mg/kg bw/day) for developmental toxicity of myclobutanil, and the adverse end-points were less critical (e.g. delayed ossification for TA at 1000 mg/kg bw/day versus reduced viability and increased resorptions for myclobutanil from 93.8 mg/kg bw/day). Therefore, it is considered that TA is not a relevant metabolite of myclobutanil. **See also comment (4)**	
(6)	Vol. 1, 2.3.5 Drinking Water Limit, pg 30 Vol. 3, B.6.10.5 Maximum acceptable	DAS: In accordance with the Annex VI Uniform Principles to 91/414/EEC (C. Decision Making, point 2.5.1.2), it is required to demonstrate that the safe level of	

<table>
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Further explanations</th></tr>
<tr><td></td><td>concentration in drinking water, pg 6-80</td><td>the active substance in drinking water is greater than the drinking water limit of 0.1 µg/L.
An extensive toxicological data base was used to set the ADI. In accordance with the International Programme of Chemical Safety (IPCS) criteria (WHO, 1994) and the EU Drinking Water Directive (98/83/EC, 1998), on the basis that exposure through drinking water should not account for more than 10% of the ADI (0.025 mg/kg bw/day), assuming an average consumption of 2 L of water/person/day and a body weight of 70 kg, a drinking water limit for myclobutanil would be 87.5 µg/L.</td><td></td></tr>
<tr><td>(7)</td><td>Vol. 1, 2.3.6 Impact on human or animal health arising from exposure to the active substance or to impurities contained in it, pg 30-31</td><td>DAS: as agreed with the RMS, a new in vitro dermal absorption study has been conducted with Systhane 20 EW (submitted to RMS, August, 2005).
Refined dermal absorption values of 5% for the formulation and 22% for the spray dilution are recommended. Based on these new data, a revised dermal absorption assessment and the revised risk assessment for operator, bystander and re-entry worker as been submitted to RMS (August, 2005)</td><td>Operator, estimation of exposure assuming PPE is not used
<table>
<tr><th>Crop-method</th><th>Dose rate L product/ha</th><th>Spray volume L/ha</th><th>Systemic exposure as % of AOEL (UKPOEM)</th><th>Systemic exposure as % of AOEL (DE)</th></tr>
<tr><td>Grapes – low volume</td><td>0.24</td><td>100</td><td>61.4</td><td>7.6</td></tr>
<tr><td>Grapes – high volume</td><td></td><td>1200</td><td>10.5</td><td></td></tr>
</table></td></tr>
</table>

No.	Column 1 Reference to Draft Assessment Report	Column 2 Comment (restricted to 500 characters)	Column 3 Further explanations
			<table><tr><td>Apples-high volume</td><td></td><td>2000</td><td>12.6</td><td></td></tr></table> **Bystander, based on highest rate for apples (worst case):** Lloyd and Bell: 0.1% of the AOEL **Worker, exposure for re-entry into the crop calculated below for grapes:** For grapes, using a transfer coefficient of 5000 cm2/hr, gives a PDE of 0.01 mg/kg bw/day, which gives the % of AOEL at 7.4 % The equivalent calculation for apples, using a transfer coefficient of 6000 cm2/hr, gives a PDE of 0.1481 mg/kg bw/day, which gives the % of AOEL value at 16.7 %.
(8)	Vol 1, List of end points Impact on Human and Animal Health Adsorption, distribution, extraction and metabolism Toxicologically significant compounds pg 61 *"Parent compound and metabolites"*	DAS: this should say 'Parent compound only': Metabolites RH-9090 and RH-9089 have comparable acute oral toxicity to myclobutanil, and have been fully evaluated in the toxicology package for myclobutanil as they are both major rat metabolites. They do no represent a toxicological concern, and do not form part of the residue definition for human health assessment and monitoring. TA is less toxic than myclobutanil and is therefore toxicologically non-significant. Please see **comment (5)**.	

section 2 - Mammalian toxicology (B.6)

No.	Column 1 Reference to Draft Assessment Report	Column 2 Comment (restricted to 500 characters)	Column 3 Further explanations
(9)	Vol 1, List of end points Impact on Human and Animal Health Dermal Absorption pg 62	DAS: the endpoints for dermal absorption and the output of the Operator Exposure modelling should be amended according to the revised calculation, **see comment (7)**	
(10)	Vol. 1, Level 4, 4.6 Toxicology and metabolism, pg 77 *"Systhane 20 EW inhalation study"*	DAS: It has been clarified with the RMS that the previously submitted study at National Level is the same acute inhalation toxicity study on Systhane 2EC, which was submitted with this dossier.	
(11)	Vol. 3, B.6.4.1.2 In vitro mammalian cell gene mutation studies Table B.6.4.1.2-1, pg 6-33	DAS: Typo: Table numbering is repeated for the 2 tables on this page	
(12)	Vol. 3, B.6.6.2.2 Teratogenicity test by the oral route in the rabbit Methodology – study acceptance, pg 6-58	DAS: Please delete the statement: "The study is accepted if the results of the range-finding study reported in the JMPR 1992 could be provided." This study has been provided in June 2005, as acknowledged by RMS at the beginning of the paragraph of pg 6-58.	
(13)	Vol. 3, B.6.8.1.1 RH9090, RH 9089 and 2 impurities Conclusion, pg 6-61	DAS: RH-9090 and RH-9089 are both plant metabolites, and not substances of their own right. Therefore, they do not come under consideration by the Dangerous Substances Directive (67/548/EEC), and would not warrant classification.	
(14)	Vol. 3, B.6.8.3 Summary of toxicity studies on metabolites and supplementary studies Triazolylalanine, pg 6-72	DAS: We do not consider TA to be a relevant metabolite of myclobutanil as its toxicity is significantly lower than the active substance itself. It is agreed that the conservative NOEL for developmental toxicity effects is 100 mg/kg bw/day. This is higher than the NOAEL (31 mg/kg bw/day) for developmental toxicity of	

<table>
<tr><th>No.</th><th>Column 1
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Comment (restricted to 500 characters)</th><th>Column 3
Further explanations</th></tr>
<tr><td></td><td>Vol. 3, B.6.10 Summary of mammalian toxicology and proposed ADI, AOEL and drinking water limit
Triazolylalanine and triazolyl acetic acid: Triazolylalanine, pg 6-78</td><td>myclobutanil, and the adverse end-points were less critical (e.g. delayed ossification for TA at 1000 mg/kg bw/day versus reduced viability and increased resorptions for myclobutanil from 93.8 mg/kg bw/day). Therefore, it is considered that TA is not a relevant metabolite of myclobutanil. See Comments (4) and (5)</td><td></td></tr>
<tr><td>(15)</td><td>Vol. 3, B.6.11.3 Acute inhalation toxicity in rats
“The company should provide this study”
Conclusion, pg 6-82</td><td><u>DAS</u>: it was clarified with the RMS that the previously submitted study at National Level is the same acute inhalation toxicity study on Systhane 2EC, which was submitted with this dossier.
Systhane 20 EW should not be classified R20: harmful by inhalation.
Based on the DPD (1999/45/EC), there is one substance in both of these formulations (cyclohexanone) which is classified R20. Cyclohexanone is present in GF-1137 preparation at 20% (w/w), and most likely causes the inhalation toxicity. The overall LC_{50} for the combined male/female data was ≥ 5.0 mg of RH-53,866 2EC per L of air.
In Systhane 20EW (the representative formulation), cyclohexanone is present at only 10% (w/w). The overall toxicity of Systhane 20EW is expected to be notably less than for GF-1137, in particular the inhalation toxicity effects.
Also, based on 91/414/EC criteria, Systhane 20EW does not meet the requirement criteria for an inhalation toxicity study (Column 3).</td><td>There is no inhalation toxicity study with Systhane 20EW. Myclobutanil was shown to have an LC_{50} >5.1 mg/L. The Notifier submitted an inhalation toxicity study with Systhane 2EC (GF-1137). The estimated female LC_{50} was > 5.0 mg/L (the highest concentration attainable) and the male LC_{50} was estimated to be >3.9 mg/L. DAS considers the overall LC_{50} for the combined male and female data was ≥ 5.0 mg of RH-53,866 2EC per L of air.

“7.1.3 Inhalation: Rationale (94/79/EC, Annex III, 7.1.3 Inhalation)”
<table>
<tr><th>The inhalation toxicity of a plant protection product must be reported where it is:</th><th>Responses</th></tr>
<tr><td>- a gas or liquefied gas</td><td>GF-1317 (Systhane 20EW) is a liquid oil in water (EW) preparation</td></tr>
<tr><td>- is a smoke-generating formulation or fumigant</td><td>GF-1317 is a liquid EW preparation</td></tr>
<tr><td>- is a vapour releasing preparation</td><td>GF-1317 is a liquid EW preparation</td></tr>
<tr><td>- is used with fogging equipment</td><td>GF-1317 is a liquid EW preparation</td></tr>
<tr><td>- is an aerosol</td><td>GF-1317 is a liquid EW</td></tr>
</table></td></tr>
</table>

No.	Column 1 Reference to Draft Assessment Report	Column 2 Comment (restricted to 500 characters)	Column 3 Further explanations	
				preparation
			- contains an active substance with a vapour pressure > 1 x 10^{-2} Pa and is to be used in enclosed spaces such as warehouses or glasshouses	The vapour pressure of myclobutanil is 1.98 x 10^{-4} Pa at 20°C
			- is a powder containing a significant proportion of particles of diameter < 50 μm (> 1 % on a weight basis)	GF-1317 is a liquid EW preparation
			- is to be applied from aircraft in cases where inhalation exposure is relevant	Application of GF-1317 is by tractor mounted or self-propelled air-assisted sprayer
			- is to be applied in a manner which generates a significant proportion of particles or droplets of diameter < 50 μm (> 1 % on a weight basis)	GF-1317 will never be applied undiluted; it will only be applied after it has been diluted in water. Based on the cGAP, the dilution will be >1000 fold (application rates of 0.28 - 0.45 litres of product/ha, spray volumes of 100 – 2000 litres/ha). It is impossible for a person to be exposed to droplets of GF-1317, instead, they may be exposed to GF-1317 in an aerosol that is at least 98.8% water. Virtually all droplets produced by air-assisted sprayers are too large to respire into the lungs (i.e., > 30 μm), the majority, if not all of a potential inhalation dose

No.	Column 1 Reference to Draft Assessment Report	Column 2 Comment (restricted to 500 characters)	Column 3 Further explanations
			that is breathed into the mouth will impact in the nasopharyngeal region and be swallowed, not inhaled.
(16)	Vol. 3, B.6.11.3 Acute inhalation toxicity in rats Materials and Methods, pg 6-82	DAS: "Systhane 20 EW" should read **Systhane 2 EC**	

section 3 - Residues (B.7)

17. – Residues (B.7)

No.	Column 1 Reference to Draft Assessment Report	Column 2 Comment (restricted to 500 characters)	Column 3 Further explanations
(1)	Vol. 1, 2.4.1 Definition of the residues relevant to MRLs, Plant products, pg 31	DAS: TA metabolite should not be considered as toxicologically relevant (see comment **(5) of Section 2 Mammalian Toxicology)** and therefore should not be included in the residue definition for wheat (or any other plant). Wheat is not included in the List of uses supported for myclobutanil.	
(3)	Vol. 3 B 7.6.2, Conclusions pg 7-33.	DAS: There is a typographical error in the STMR indicated for grape trials in the South (SZ). The document indicates that the STMR is 0.043 mg/kg. However, **the correct STMR should be 0.052 mg/kg**, based on the 14 trial results considered, which are 0.063-0.043-0.09-0.04-0.10-0.13-0.02-0.03-0.09-0.03-0.06-0.02-0.10-and- 0.02 mg/kg.	
(4)	Vol. 3 Table B7.7.2-1, pg 7-34.	DAS: in the title of the table the following phrase is included: "(Residues expressed as mg myclobutanil equivalents/kg)". The word "equivalents" should be removed from this phrase since it is only myclobutanil residues (not metabolites) that are reported here.	
(5)	Vol. 3 Table B7.8.1-1, pg 7-37	DAS: the heading in column 1 should be changed from "Metabolites" to "Analytes". Myclobutanil is included as one of the analytes and should not be referred to as a metabolite.	

18. Environmental fate and behaviour (B.8)

No.	Column 1 Reference to Draft Assessment Report	Column 2 Comment (restricted to 500 characters)	Column 3 Further explanations
(1)	Vol. 1, B.2.5.2, Fate and Behaviour in soil, Lysimeter study, pg 33	DAS: this point was discussed with the RMS during the preparation of the DAR and the agreed conclusion was that a lysimeter study **is not necessary** and that this requirement was not to be included in the DAR as it is stated in Vol. 3, point 8.2.4. pg 8-18 of the DAR: "*We have considered that a lysimeter study would not be necessary: sufficient lab data to determine the PEC, several scenarios are acceptable"*	The PECgw calculations for a worst case GAP clearly indicate that the risk to groundwater is acceptable for several FOCUS scenarios. For some scenarios the PECgw values are above or very close to the trigger of 0.1 µg/L. However, for Annex I, it is not necessary to pass every FOCUS scenario. In principle, only one scenario needs to pass and this is clearly the case for both myclobutanil and the "butyric acid" metabolite for both the apples and vines uses. Therefore, it is not necessary to carry out a lysimeter study. Furthermore, lysimeters would not be considered appropriate or practical for a 3-D crop like apples or vines
(2)	Vol. 1, 2.5.3 Fate and behaviour in water impact on water treatment procedures, pg 34	DAS: typo: change metconazole to myclobutanil	
(3)	Vol 3. B.8.1.1.2 Anaerobic degradation in soil, pg 8-10 Vol 3. B.8.1.2.2 Anaerobic degradation, pg 8-13	DAS: the statement "no acceptable study" it is not appropriate: the study is simply not required.	An anaerobic study was provided by DAS. Although lacking in some respects, the submitted study was deemed acceptable by DAS in showing that anaerobic degradation will not be a significant route of degradation for myclobutanil. However, we accept the Rapporteur's point that under normal conditions of use (fungicide in vines and apples), it is not expected that myclobutanil will be exposed to anaerobic conditions.
(4)	Vol. 3 B.8.1.3.1 Soil dissipation testing, pg 8-13	DAS: the soil dissipation data have been summarized separately in an appendix while it would be more consistent to include the DT50 values in the main body of the document as with the lab data.	

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

No.	Column 1 Reference to Draft Assessment Report	Column 2 Comment (restricted to 500 characters)	Column 3 Further explanations
(5)	Volume 3 B.8.3 Predicted environmental concentration in soil (PECs) pg 8-19	DAS: The initial PECs values reported in the DAR are slightly lower to those calculated by DAS (0.126 and 0.236 mg/kg *vs.* 0.128 and 0.240 mg/kg for vines and apples, respectively). DAS believes this to be an error because the RMS subsequently used 0.128 and 0240 mg/kg as the initial PECs values in the accumulation PEC table and calculation. Also, DAS considers that it is more consistent to use the mean lab DT50 for the TWA calculations, rather than the worst case.	
(6)	Vol 3 B 8.6.2 Predicted environmental concentrations in surface water PECsw pg 8-33	DAS: Under the PECsw and PECsed calculations: DAS believes that it is inappropriate to use spray drift tables as the primary method of aquatic exposure assessment. This is because the FOCUS sw scenarios have been prescribed for use in the aquatic risk assessment for List 3A molecules.	

section 5 - Ecotoxicology (B.9)

19. Ecotoxicology (B.9)

No.	Column 1 Reference to Draft Assessment Report	Column 2 Comment (restricted to 500 characters)	Column 3 Further explanations
(1)	Vol. 1, 2.6.3 Effect on other arthropods, pg 37 Vol. 3 B.9.5.4 Risk assessment for non-target arthropods, pg 9-57	DAS: DAS agree with the RMS that myclobutanil poses an acceptable risk to terrestrial non-target arthropods. However, as the DAR is intended to meet the requirements of safe uses according to 91/414/EEC the comment relating to additional testing at the MS level seems inappropriate *as no risk to non-target arthropods has been identified*. DAS do recognize that each MS may have its own local requirements but this is beyond the scope of the DAR and request that the comment be removed.	
(2)	Vol. 3, B.9.2.2 – Fish juvenile growth test, p. 9-15	DAS: The use of the chronic endpoint from the rainbow trout 21-day chronic study is inappropriate for risk assessment purposes since the study was not performed at a high enough concentration to produce a LOEC. Therefore, the NOEC from this study is an artifact of the study concentrations and is not accurate. The true NOEC for chronic effects of myclobutanil on fish should be from the fish early life-stage toxicity test with the fathead minnow (B 9.2.3). The fish early life-stage toxicity test is also a more sensitive test than the 21-day study. Therefore, the endpoint is more robust. **The correct endpoint is 0.98 mg a.s./L.**	
(3)	Vol. 3, Refined risk assessment for the long-term exposure of small herbivorous mammals, pg 9-40	DAS: For the refinement of the risk assessment for long term effects on mammals in orchards, a foliar interception factor of 70% was used for foliage development. It should be made clear that the risk assessment presented in the dossier shows that applications can be made at an earlier stage than foliar development, that being at flowering. Using an interception factor of 65% for flowering, the risk assessment must be taken one more step, but acceptable risk is shown in the dossier for 2 applications at flowering and 2 at foliage development. **DAS would like to make it clear that applications can be made to orchards at the flowering stage.**	

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

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

20. Environmental fate and behaviour (B.8)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B 8. 3, Predicted environmental concentration in soil (PECs); and Vol. 3, B. 8. 6. 1., Predicted environmental concentration in groundwater (PECgw)	PL: For the calculation of PEC_S the highest soil DT_{50} value was used, while for the calculation of PEC_{GW} the mean values (two times lower) were used. Could you please explain the reasons for such choice (as it seems to be inconsistent).	

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

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.2.2.19 shelf life	AT: It should be discussed in an expert meeting, whether the content of the relevant impurity should be determined in the formulation, since it is described as result of incomplete removal of a solvent in the production process of the a.s. and the increase during storage seems unlikely.	
(2)	Vol. 3, B.2.2.32 pourability	AT: The value for the residue should be max. 5%. The value for rinsed residue is missing.	
(3)	Vol. 3, B.5.1.4 analytical method, relevant impurity in the formulation	AT: see number (1)	
(4)	Vol. 3, B.5.3.2 analytical method, residue in water	AT: A linearity range of 0.15 to 12.5 µg/L seems unreliable to cover a range of fortification levels of 0.05 to 50.0 µg/L. The numbers of samples for each fortification level are not in accordance with guidance document 825/00.	
(5)	Vol. 3, B.5.3.3 analytical method, residue in air	AT: The breakthrough behaviour is not reported.	
(6)	Vol. 4, C.1.3 composition of the formulation	AT: A detailed composition of GF-1062 is required, since it is described under B.2.2 as similar to GF-1317. If RMS confirm the analogousness (except the replaced co-formulant), this point is superfluous.	

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22. 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. #, <<data point>>, <<description>>	<<MS/notifier>>: <<comment>>	

section 3 - Residues (B.7)

23. Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 1, 2.4.1, Definition of residues	AT: No residue definition for food of animal origin has been proposed by the RMS, since the intake based on residues found in possible feed according to the intended uses is not regarded relevant. Nevertheless, metabolism studies on laying hen and lactating cows have been provided and evaluated. After a possible annex 1 inclusion of this substance, additional uses may be supported by the notifier; a proposal for the residue definition of animal origin is therefore very helpful to be peer reviewed.	

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

24. 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, route of degradation in soil and Vol.3, B.8.1.1.1 Aerobic degradation in soil, Table B.8.1.1.1-5	AT: Did the metabolite Myclobutanil butyric acid exceed the 5 % level only once (76 d) or at several consecutive time points? If the metabolite accounts for more than 5 % in at least two sequential measurements its relevance must be assessed (according to Guidance Document on the assessment of the relevance of metabolites in Groundwater).	
(2)	Vol. 1, list of endpoints, rate of degradation in soil, laboratory studies	AT: The DT50-values (DT50 = 5-42 d at 25°C) of the metabolite Myclobutanil butyric acid (max. 6 %, 76 d) determined by a separate study should be mentioned in the list of endpoints	
(3)	Vol.1, list of endpoints, route of degradation in soil – supplemental studies, soil photolysis and Vol. 3, B.8.1.1.3. soil photolysis	AT: The study showed many deviations from the current guidelines; especially the light intensity of 21 W/m^2 was too low and the range of the light source of 290 – 480 nm was too small. Can this study really be accepted as valid and is the photodegradation of the active substance really clarified with this study? If not, a new study has to be conducted/provided. The deviations should be mentioned in the list of endpoints.	

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

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(4)	Vol.3, B.8.1.3.1 Soil dissipating testing and Vol. 3, B.8.1.3.2. soil residue testing –soil accumulation testing and Appendix 1 – field studies	AT: Was the metabolite RH9090 (putative photolytic metabolite) the only metabolite investigated although the metabolites RH9089 and Myclobutanil butyric acid seemed to occurre in higher amounts than RH9090 during the studies in laboratory? Is there any explanation given for this selection?	
(5)	Vol.1, list of endpoints, soil adsorption/desorption and Vol.3, B.8.2.1 Adsorption and desorption	AT: The Kd- and Koc-values of the metabolite Myclobutanil butyric acid should be mentioned in the endpoint list.	
(6)	Vol.1, list of endpoints, PECgw	AT: The PECgw-values for the metabolite Myclobutanil butyric acid should be mentioned in the endpoint list.	

section 5 -Ecotoxicology (B.9)

25. Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.9.2.8 Effects on algal growth	AT: For the acute toxicity study with *Scenedesmus subspicatus* (Ellgehausen, 1987) only the E_bC_{50} – endpoint is mentioned. In our opinion, also the E_rC_{50} – endpoint should be reported.	
(2)	Vol. 3, B.9.7 effects on other soil non-target macro-organisms	AT: The evaluation of the two litter-bag studies should be consistent. The first study (Galicia, 2002) was not considered valid as no effects were observed in the positive control. The second study (Mallet, 2004) was accepted, though even no positive control was tested. We think that this is contradictory and a short comment to address this issue should be included. Further, a final conclusion/risk assessment on the results of the litter-bag studies should be added.	
(3)	Vol. 1, LOE Toxicity data for aquatic species	AT: The endpoints for the formulation used in the risk assessement should also be highlighted in bold.	
(4)	Vol. 1, LOE Hazard quotient for honey bees	AT. The hazard quotients should be given as </> values in accordance with the toxicity endpoints.	
(5)	1, LOE Non-target plants	AT: “Effects on non-target plants” are missing in the LOE.	

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26. 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. #, <<data point>>, <<description>>	<<MS>>: <<comment>>	

27. 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.6.10.4, AOEL	DK disagrees with the proposed AOEL. We propose to base the AOEL on the NOAEL from the long-term rat study where effects are seen on the testes at 9.8 mg/kg/d already after 1 year. And as the effects are serious we propose to use a SF of 300. I.e. the AOEL will be 0.03 mg/kg bw/d.	
(2)	Vol. 3, B.6.12, dermal absorption	DK finds that the estimated dermal absorption is too low. In table B.6.12.1-4 is stated that the absorption is the sum of urine and faeces excretion and taken into account the excretion after i.v. application. But the figures in the table are only based on urinary excretion and the amount in the skin is not included. In the other study the exposure for the concentrate is even higher. We propose to discuss the absorption in an expert meeting.	
(3)	Vol. 3, B 6.15.1, operator exposure	We would like to see the exposure recalculated with the lower AOEL we have proposed.	

section 3 - Residues (B.7)

28. 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. #, <<data point>>, <<description>>	<<MS>>: <<comment>>	

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

29. 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.8.6.2 PECsw – FOCUS	DK: What is the purpose of presenting PECsw where only drift is considered?	
(2)	Vol. 3, B.8.6.2 PECsw – FOCUS	DK: Results from step 1 & 2 of the FOCUS PECsw estimation is missing in the DAR	
(3)	Vol. 3, B.8.6.2 PECsw – FOCUS	DK: The version of FOCUSsw software used for step 3 and 4 is not given the text or tables.	

section 5 - Ecotoxicology (B.9)

30. Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(1)	Vol. 3, B.9.2, Aquatic risk assessment	DK: The results of the risk assessment applying FOCUS step 1 and 2 should be presented.	

31. 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, list of end points, minimum purity, p. 39 in relation to Volume 4	EFSA: According to Directive 94/37/EC the ratio of the content of the isomers must be provided. It seems that this information is not reported in the DAR. Furthermore, is the assumption correct that both isomers have the same biological activity, due to the fact that nothing else is mentioned?	
(2)	Vol. 3, B.2.1.23 surface tension, p. 2-9	EFSA: Being aware that in EEC A5 is stated that the described methods are applicable to most substances "without any restriction in respect to their degree of purity", it should be confirmed that a possible influence of the impurities was considered by the interpretation of the measured value.	
(3)	Vol. 3, B.2.2.16 shelf life, p. 2-15f	EFSA: Taken into account that the RMS has identified one relevant impurity, it should be clarified whether or not data are available to demonstrate that the relevant impurity in the technical material are not increasing in the formulation upon storage.	
(4)	Vol. 3, B 3.6 references relied on, p. 3-13f	EFSA: It seems that none of the mentioned studies is quoted in chapter 3. Furthermore, why are only references for two annex points given? Where is the other information coming from?	
(5)	Vol. 3, B.5.2.1 plant origin, p. 5-7	EFSA: The RMS should clarify the acceptability of the multi-method, since the reported LOQ is too high according to the criteria of SANCO/825/00 and Annex VI.	It seems that the German multi-method (L.00.00-34, extension version of S19) has been validated properly.

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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. 3, B 5.6 references relied on, p. 5-18f	EFSA: It should be noted that the methods for the determination of residues in food of animal origin should not be listed here, since no MRLs are proposed and therefore an important parameter is missing to assess the methods. Consequently it is not possible to rely on them.	

32. 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)	General comment	EFSA: the declared minimum purity of myclobutanil is 925 g/kg. Many of the key toxicological studies were conducted with different purities (81.1%, 84.5%, 90.4%, etc). The relevance of the outcomes of the studies on the overall risk assessment has to be commented by the RMS. Furthermore, the applicant mentions (see comments on the draft assessment report) a "new package of acute toxicity studies conducted with myclobutanil technical grade from the actual registered source". It should be clarified whether the new studies are available and whether the tox data presented in the DAR are applicable also to the new source	
(2)	Vol. 1, lev. 4, point 4.1	EFSA agrees with the RMS's data requirement on the impurity profile with regard to the impurities 3 and 8	
(3)	Vol. 3, B.6.8.3 Summary of toxicity studies on metabolites	EFSA: According to the residue scientific check (see comment 9), metabolites RH9090 and its glucoside should be included in the residue definition. Their toxicological relevance for the consumers should be addressed (the only available information show that the acute oral toxicity of metabolite RH 9090 is comparable to that of myclobutanil).	

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
(4)	Vol. 3, B.6.9.1 Report on medical surveillance on manufacturing plant personnel	EFSA: information provided are poor, only 15 workers considered. Considering that the substance is used since a long time and that ECB classified it already in 1997, it cannot be considered sufficient.	
(5)	Vol. 3, B.6.12 Dermal absorption	EFSA: both *in vivo* studies show some drawbacks. In the DAR, a new ongoing *in vitro* study is mentioned. It should be clarified whether it is available.	
(6)	Vol. 3, B.6.15 Exposure data	EFSA notes that in case dermal absorption values are revised, a re-calculation of the operator, worker and bystander exposure has to be provided.	
(7)	Vol. 3, B.6.15.1 Estimation of operator exposure	EFSA: Work rate considered is15 hectares per day. It's not clear whether this value was applied to both German and UK POEM scenario. In this case, the operator exposure calculated with the German model would be overestimated, since the default treated area for high crop is 8 ha.	
(8)	Vol. 3, B.6.15.1 Estimation of operator exposure	EFSA: in the table B.6.15.1-1, the pack size indicated is 1.5 L, which is not in accordance neither with what is reported in the B3 nor with the calculation appendix. RMS to clarify	
(9)	Vol. 3, B.6.15.1 Estimation of operator exposure	EFSA notes that a body weight of 60 kg is considered for both UK POEM and German model (the default considered in the German model is 70 kg).	

section 3 - Residues (B.7)

33. 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, List of end points, summary of representative uses	EFSA: For confirmation: is it correct that the representative use for NEU is in table and wine grapes.	
(2)	Vol. 3, B.7.1.1 Grapes metabolism study: Nelson S.S., 1984(a)	EFSA: (1) This metabolism study investigating the uptake via roots is not relevant for the representative use (foliar application). Moreover, the information provided in this study is of limited value as it is not clear which parts of the grape seedlings have been analysed and the concentration of myclobutanil equiv. in mg/kg is not provided. Consequently, the reference should be deleted in the list of studies relied on. The metabolism study in grapes has the same reference (Nelson S.S., 1984a). If the study for grapes is deleted as it is not relevant for the supported use, no further changes are necessary in Annex B. In order to distinguish the two studies, the reference has to be changed in Annex A of the DAR to Nelson S.S. 1984b.	
(3)	Vol.3, General comment for all metabolism studies	EFSA: Please provide information on the radioactive purity and the specific activity of the test substance.	
(4)	Vol. 3, B.7.1.1 Grapes metabolism study: Nelson S.S., 1984(b)	EFSA: (1) The RMS mentioned that the extraction pathway for whole grapes was missing. To our understanding, the grapes were first separated into	

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section 3 - Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		juice and pomace, and then extracted separately. On the basis of the weight of the juice and pomace fractions the identified compounds were recalculated to whole grapes. (2) The concentration and percentage of residual radioactivity (non extractable residues) for juice and whole grapes should be provided in order to decide whether further attempts to release the radioactivity and characterise/identify the components are required. (3) The total radioactive residue concentrations are provided for wet and dried pomace, but it is not clear whether the values for the methanol extraction phase and the subsequent partition in hexane and chloroform are related to wet or dry pomace. (Most likely the values are for wet pomace, please confirm) The same applies for the identified metabolites. Are they calculated for wet or dry pomace?	
(5)	Vol. 3, B.7.1.2 Metabolism study in apples , Nelson S.S., Streelman DR, 1984c	(1) Apple pomace was first extracted with methanol. Please provide the myclobutanil equiv. concentration and the TRR% for this fraction (before the partitioning). (2) Please provide the information on the residual radioactive residues in the last row of the table on page 7-6. According to the second paragraph on page 7-7, more than 52% and 73% of TRR could be extracted. As the trigger values for characterisation/identification of metabolites might be exceeded, the notifier should provide	

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		information on attempts to release, characterise and identify the non extractable residues.	
(6)	Vol. 3, B.7.1.3 Metabolism study in wheat (Nelson S.S. 1984a)	(1) How many days after the last application was the sampling? Is there an explanation for the different myclobutanil concentrations in straw under field and greenhouse conditions? (Maybe different PHI?) (2) What was the residual radioactive residue concentration in grain (field and greenhouse conditions, phenyl label) and straw (field and greenhouse condition, triazole and phenyl label, respectively). (3) EFSA shares the view of the RMS that the cleavage of the molecule in wheat is likely. The argument provided by the notifier that in case of cleavage of the molecule metabolites containing only the phenyl ring moiety would arise is true, but as about 50 % of extracted TRR in grain were not identified and probably about 50% of TRR were not extractable it cannot be excluded that phenyl-metabolites are present in these fractions.	
(7)	Vol 3, B.7.1.3 Metabolism study in cows (Jacobson A.H. 1986b)	EFSA: (1) For compounds with multiple ring structures usually separate metabolism studies reflecting labelling of each ring is required, unless the cleavage of the ring systems can be excluded. In addition, the metabolism study should be performed not with a mixture of active ingredients	

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
		and plant metabolites. Only the parent should be fed. Did the notifier provide a rationale for this study design deviating from the general approach? Due to this study design for example it would not be possible to identify metabolites containing the triazol ring after cleavage as the precursor molecule (parent compound) was only labelled in the phenyl ring. (2) The log Pow provided in the list of end points for the parent compound is different (2.89). Are there log Pow values available for the metabolites? (3) Calculation of the dietary burden: see comment no. (13) (4) Please provide detailed information on the extraction pathway and the subsequent partitioning in solvents systems. Did the identified metabolites occur in the water or in the organic phase? (5) In table B.7.2.1-3 the RMS reported the percentage of the total radioactive residues. Can you please report also the concentration of myclobutanil equiv. in mg/kg. (6) What are residues of myclobutanil related metabolites in muscle? (7) In the conclusion the RMS mentions that carboxylic acid RH-294 was formed after hydroxylation of RH.9090. According to the metabolic pathway in figure 2 RH-294 is a diol and not a carboxylic acid.	

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
(8)	Vol. 3, B.7.1.4 Metabolism in hens, Table 7.2.2-3	EFSA: (1) Please provide detailed information on extraction pathway (which solvents were used, which extracts were used for further partitioning?). (2) In table B.7.2.2-3 metabolites were identified as lactone metabolite and undissociated lactone/RH9090/RH9089. Please specify what exactly is meant.	
(9)	Vol 3, B.7.3 Residue definition for plant products	EFSA agrees with the proposed residue definition for monitoring for the uses in fruit, but disagrees with the proposal for risk assessment. According to the metabolism studies in apples ca 35 % of TRR were identified as RH-9090 and RH-9090 glucoside. For grapes the percentage was about 15%. If these metabolites are not taken into account, the consumer risk might be underestimated. The proposed residue definitions are only valid for fruit crops. According to the metabolism study in wheat additional metabolites might be included in the residue definition. However, for these metabolites the toxicological relevance has to be clarified.	
(10)	Vol 3, B.7.4 Residue definition for animal products	EFSA: If residues above the trigger values of 0.1 mg/kg feed (DM) are expected a residue definition for animal products should be proposed. In addition it should be clarified whether the residues are water or fat soluble. The RMS states that	

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
		myclobutanil residues should be considered as non liposoluble due to the log Pow of the parent compound. However, no information is available on the log Pow of the metabolites. In the cow metabolism study only metabolites were observed, no parent compound was not detected in any tissue of the cow and in milk.	
(11)	Vol. 3, B.7.7.1 Effects on the nature of residues	EFSA: A study investigating the effects on the nature of residues has to be provided. The justification for not providing the study is not acceptable.	
(12)	Vol. 3, B.7.7.2 Effects on the level of residues	EFSA: The study is of limited validity as no information on the nature of potential metabolites generated during processing is available. A final conclusion is pending the outcome of the study on the effects on the nature of residues. Is there a reason why in two of the processing studies the transfer factors for wet pomace was lower than 1 (indicating that the residues would be diluted). Please provide a statement on the acceptability of this studies?	
(13)	Vol. 3, 7.8 Livestock feeding study	EFSA: The calculation of the dietary burden for cattle should be based on the results of the residue trials in apples and the processing factor for apple pomace. In this case, the STMR of the apple trials (0.142 mg/kg) and the processing factor proposed by the RMS (2.97) gives 0.42 mg/kg in wet pomace. The dietary burden for beef cattle results in 0.55 mg/kg feed (DM) or 0.023 mg/kg bw.	

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section 3 - Residues (B.7)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
		From metabolism studies in cows it was concluded that one of the main metabolites in animal products was 4-hydroxy-3-lactone (46% and 22% in liver and kidney, resp.). In the feeding study this compound was not analysed. What is carboxylic acid RH-0294? According to the metabolic pathway presented in Figure 2 (page 7-61) RH-294 is a diol, but does not contain a carboxylic group.	
(14)	Vol. 3, 7.8.1 Livestock feeding studies in lactating cows or goats	EFSA: Considering the revised dietary burden calculation with the STMR from apples and the average processing factor, the lower dose group in the feeding study 1.6 mg/kg bw/day represents a 3 fold dose rate. The statement in the conclusion should therefore be amended accordingly.	
(15)	Vol. 3, B.7.11.2 Short term dietary intake risk assessment	EFSA: In general, the risk assessment for processed commodities like wine should be calculated with the STMR on grapes (0.12 mg/kg for NEU), multiplied with the average processing factor (0.128), respectively. The same calculation has to be performed for apple juice. However, the final result will not be influenced significantly.	
(16)	Vol. 3, B7.16 References relied on	EFSA: The study Betteley, 1994 is not relevant and should be deleted from the list of studies relied on.	

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

34. 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, general	EFSA: Please add to the endpoints sheet the endpoints for the metabolite myclobutanil butyric acid (degradation rates, adsorption, groundwater PEC)	
(2)	Vol 1, list of endpoints, Anaerobic degradation, p.45	EFSA: Please state 'no acceptable study, not required for the representative uses evaluated'	
(3)	Vol 1, list of endpoints, Rate of degradation in soil, method of calculation, p.45	EFSA: The appropriate information needs to be added to this box. I.e first order linear regression, or first order non-linear regression, field studies biphasic first order etc.	
(4)	Vol 1, list of endpoints, Rate of degradation in lab soil, DT50 values, p.45	EFSA: Please also add the FOCUS normalised geomean value of 250 days that has been used in some (the most recent) FOCUS groundwater modelling as well as the arithmetic mean value that is currently listed, that has been used for the FOCUSsw modelling.	
(5)	Vol 1, list of endpoints, Photochemical oxidative degradation in air, p.53	EFSA: Please state the OH concentration assumed for the calculation..	

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
(6)	Vol. 3. B.8.2.1, adsorption/desoprtion p. 8-16 Vol 1, list of endpoints, adsorption/desorption, p.46	EFSA: Based on such a small data set it is unlikely that the correlation identified for Kf with CEC and pH regarding parent myclobutanil is real. Also for a compound with a pKa of 2.3 there is no first principles reason to expect any correlation with soil pH. If as rapporteur you are convinced the correlations are real these should be taken into account for PEC groundwater (and possibly surface water) calculations at the first tier of assessment.	Taking such real correlations into account in a groundwater assessment is not a refinement step, it is necessary at the first tier to ensure the assessment retains the appropriate level of precaution. If the correlations are not real then the existing PECgw using mean values are appropriate at the first tier of assessment.
(7)	Vol. 3. B.8.2.1, adsorption/desoprtion p. 8-17	EFSA: Study on soil batch equilibrium adsorption/desorption of myclobutanil butyric acid has the study author and date missing. Presumably this study was Smith J.K. 2004? Please clarify this.	
(8)	Vol 3, B.8.3, PECsoil p 8-19-20 Vol, List of endpoints PECsoil p 47-48	EFSA: The EFSA can agree to the use of the longest single first order laboratory DT50 for myclobutanil of 574 days to calculate an accumulated PEC in soil. However field data would probably provide a more realistic estimate. For the available field data to be used as the basis for PEC soil calculation, a new kinetic assessment of the field studies that accurately estimated the biphasic DT90 (which is currently not available) would be required.	

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.8.4.4, Water sediment study p. 8-23-26 Vol 1, list of endpoints, Route and rate of degradation in water, p.48	EFSA: Two sediment water systems were studied. Only a degradation endpoint (whole system) for 1 system is reported in the endpoints. Values for both systems should be reported (even if for the second system just a graphical estimate is reported, although first order non linear regression can be made to provide a reasonable fit (first order DT50 805 days r^2=0.786) if samples at day 1 and 2 are treated as outliers). Also if a long value (805 / 838 days) is not included in the endpoints it is unclear where the value used in FOCUS sw modelling (626 days, presumably the arithmetic mean of 415&838 days) comes from. Arguably a less precautionary geomean value of 578 days (from 415 & 805 days) could have been used for FOCUSsw modelling (surrogate sediment input value).	
(10)	Vol 3, B.8.6.2, PECsw p. 8-30-32 Vol. 1, List of endpoints PECsw p. 49	EFSA: The simply calculated spray drift PEC should not have been presented as FOCUSsw approaches are available and are required for the assessment. The FOCUSsw values should be in the list of endpoints. As the FOCUSsw aquatic exposure assessment has drift as the predominant route of entry, was it checked that a single application (with the resulting higher spray drift %) did not result in higher global maximum PECsw than the multiple application simulations currently reported? As the modelling used a very long sediment half life (626 days) was it confirmed that accumulation in sediment from use over	Calculating a single application event as well as the 4 applications is necessary to comply with FOCUSsw guidance. If this was done please could a statement to this effect be provided. If it was not done then this should be checked. Multiple applications may well only represent a worst case for the PECsw in ponds? For PECsed the 4 applications will represent the worst case but the potential for accumulation in sediment from applications over several

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

<table>
<tr><th>No.</th><th>Column 1
Reference to draft assessment report *</th><th>Column 2
Comment * (restricted to 500 characters, ca.10 lines)</th><th>Column 3
Further explanations</th></tr>
<tr><td></td><td></td><td>successive years is not an issue for this substance? See section 8.7.3 page 217 of SANOCO/4802/2001 rev.2 final (May 2003), where this issue is discussed.</td><td>years also has to be considered when significant partitioning to sediment is expected and the substance is persistent in sediment, as in this case.</td></tr>
<tr><td>(11)</td><td>Vol 3, B.8.6.1, PECgw p 8-26-29
Vol. 1, List of endpoints PECgw p 52-53</td><td>EFSA: What were the crop interception values used when defining the soil application rate used in simulations? Please report the kinetic formation fraction that was used in the PECgw calculation for mycolbutanil butyric acid. Clarify how the normalised geomean butyric acid DT50 of 10 days was calculated. The value EFSA calculated is 15.6 days? Please specify what the difference in the input values (application timing and crop interception) used to produce the ‘realistic case and worst case’ results reported were.</td><td><table>
<tr><td>First order DT50 soil butyric acid metabolite</td><td></td><td></td><td></td><td></td><td>geomean</td></tr>
<tr><td>25°C and 1/3 bar moisture</td><td>7</td><td>5</td><td>22</td><td>42</td><td></td></tr>
<tr><td>20°C and -10kPa moisture</td><td>8.2</td><td>7.3</td><td>21.8</td><td>45.6</td><td>15.6</td></tr>
</table></td></tr>
<tr><td>(12)</td><td>Vol 3, B.8.6.1, PECgw p 8-26-29
Vol, List of endpoints PECgw p 52-53</td><td>EFSA: Modelling is only presented using the model FOCUS PELMO 3.3.2. In line with the EFSA PPR Panel opinion of September 2004 (question No 2004-58) the modelling exercise should be repeated using the PEARL model.</td><td></td></tr>
</table>

section 5 - Ecotoxicology (B.9)

35. 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 General	EFSA: A full specification of the material used in all studies should be provided by the applicant and the compliance with the specification of the technical material should be assessed.	Annex IIA in 91/414 8. Ecotoxicological studies Test substance (vi) A detailed description (specification) of the material used, as provided for under point 1.11 must be provided. Where testing is done using active substance the material used should be of that specification that will be used in the manufacture of preparations to be authorized except where radiolabelled material is used.
(2)	Vol. 3, B.9.1.1 and B.9.1.2; Acute oral and dietary toxicity to birds, p.401	EFSA: It is noted that the purity of the technical material used in the studies was only 84.5% while the technical specification is 92.5%. This seems not to have been considered.	
(3)	Vol. 3, B.9.1.2 Avian dietary toxicity	EFSA: For what period was the mean food consumption and body weights calculated?	
(4)	Vol. 3, 9.2.9 Effects on sediment dwelling organisms, p. 9-27	EFSA: We propose to use the NOEC of 4.98 mg a.s./L derived in the study and compare it with the PEC sw value since it was a water spiked study.	
(5)	Vol. 3, B.9.2.16; Exposure and risk assessment for aquatic organisms	EFSA: Please check that a single application (with a higher spray drift %) doesn't give rise to higher PECsw (see EFSA comment in fate section). Should these PECsw values be worst case, please calculate new TER values.	

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, B.9.2.16; Exposure and risk assessment for aquatic organisms	EFSA: It is stated that the acute risk is acceptable since all TER values are exceeding the trigger value. However, risk mitigation is required in 8 out of 10 scenarios. This should be indicated more clearly. Tables like the one agreed for the list of endpoints EPCO No E 4, revision 4 (September 2005) could preferable be used.	
(7)	Vol.3, B.9.5.4; Summary of effects to NTA	EFSA: The dose rates applied in the first tier studies with *T. pyri, A. rhopalosiphi, Coccinella* and *Pardosa* do not cover the maximum application rate in apples, and not in vine either if a multiple application factor is considered. Since the studies were not of a dose-response design, no LR_{50} could be derived and consequently no HQs were calculated. However, since effects were observed and the dose rates didn't cover the proposed uses, further studies with *Coccinella* are considered necessary in addition to the available semi-field and field studies with *T. pyri* and *A. rhopalosiphi.*	
(8)	Vol. 3, B.9.9.6.3, Acute toxicity of the formulation to earthworms	EFSA: It is noted that the in the acute formulation toxicity study with earthworms Systhane 24E was used. However since a reproduction study with the lead formulation is available the results from this study can be used to assess the risk from the formulation.	

section 5 - Ecotoxicology (B.9)

No.	Column 1 Reference to draft assessment report *	Column 2 Comment * (restricted to 500 characters, ca.10 lines)	Column 3 Further explanations
(9)	Vol. 3, B.9.6.6 Risk assessment for earthworms	EFSA: At least for the first tier risk assessment the peak PEC_{soil} following the last application on top of the accumulation plateau should be used regarding the risk for soil organisms in case that there are several applications foreseen (Agreed in EPCO 17, Jan-Feb 2005). Please calculate new TER values.	
(10)	Vol.3, B.9.7; Effects on other soil macro-organisms	EFSA: A litter bag study is triggered based on the persistence of myclobutanil in soil. It is not clear why the study by Galicia (2002) was stated not acceptable while the study by Mallet (204) is considered acceptable. A positive control is lacking in both studies and it is not clear if the concentrations in soil at the start of the study covered the long-term pluriannual plateau over years plus the additional application for the season.	
(11)	Vol.3, B.9.7; Effects on other soil macro-organisms	EFSA: In the risk assessment for *Folsomia* the PEC_s from long-term pluriannual plateau over years plus the additional application for the season should have been used. TER values would however still be above the trigger.	

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
(12)	Vol.3, B.9.8.2, Impact of the formulation on soil microbial activity	EFSA: It was noted that the study on effects on soil microbial activity used the formulation Systahane 24E. Nothing is stated about the comparability with the lead formulation. It was also noted that the application rate just covers the peak PEC_s but no exaggerated dose rate was tested. We consider this as necessary especially for persistent substances as myclobutanil.	
(13)	Vol. 1, List of endpoints, General	EFSA: Please use the EPCO No E 4, revision 4 (September 2005) template for the list of endpoints and fill in results for all groups of organisms where relevant.	
(14)	Vol. 1, List of endpoints, Effects on other arthropod species	EFSA: Please report % effects on mortality and reproduction instead of reduction in beneficial capacity. Please also report the effects based on dose rate of a.s./ha. For the extended tests the 50% trigger value is from ESCORT II and not from Annex VI.	
(15)	Vol. 1, List of endpoints, Effects on other arthropod species	EFSA: Please add information on crop, application interval and location (for the field study) in the box for field or semi-field studies.	