CONCLUSION ON PESTICIDE PEER REVIEW

Conclusion on the peer review of the pesticide risk assessment of the active substance myclobutanil[1]

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SUMMARY

Myclobutanil is one of the 79 substances of the third stage Part A of the review programme covered by Commission Regulation (EC) No 1490/2002.[3] This Regulation requires the European Food Safety Authority (EFSA) to organise a peer review of the initial evaluation, i.e. the draft assessment report (DAR), provided by the designated rapporteur Member State and to provide within one year a conclusion on the risk assessment to the EU-Commission.

Belgium being the designated rapporteur Member State submitted the DAR on myclobutanil in accordance with the provisions of Article 10(1) of the Regulation (EC) No 1490/2002, which was received by the EFSA on 4 July 2005. The peer review was initiated on 29 March 2006 by dispatching the DAR for consultation of the Member States and the sole applicant Dow AgroSciences. Subsequently, the comments received on the DAR were examined by the rapporteur Member State and the need for additional data was agreed on during a written procedure in October – November 2006. Remaining issues as well as further data made available by the notifier upon request were evaluated in a series of scientific meetings with Member State experts in March 2007.

A discussion of the outcome of the consultation of experts took place with representatives from the Member States on 14 November 2007 leading to the conclusions set out in the EFSA conclusion finalised on 4 June 2009 (EFSA scientific Report 2009 (298)).

Following the Commission Decision of 5 December 2008 (2008/934/EC)4 concerning the non-inclusion of myclobutanil in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing that substance, the applicant Dow AgroScience made a resubmission application for the inclusion of myclobutanil in Annex I in accordance with the provisions laid down in Chapter III of Commission Regulation (EC) No. 33/20085. The resubmission dossier included further data in all section.

In accordance with Article 18 of Commission Regulation (EC) No. 33/2008, Belgium, being the designated rapporteur Member State, submitted an evaluation of the additional data on myclobutanil in the format of an Additional Report (Belgium, 2009). The Additional Report was received by the EFSA on 22 October 2009.

1 On request from the European Commission, Question No EFSA-Q-2010-00035, issued on 11 July 2010.

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3 OJ No L 224, 21.08.2002, p. 25, as amended by Regulation (EC) No 1095/2007 (OJ L 246, 21.9.2007, p. 19)

4 OJ No L 295, 04.11.2008, p.53

5 OJ No L 295, 04.11.2008, p.53

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In accordance with Article 19, the EFSA distributed the Additional Report to the Member States and the applicant for comments on 26 October 2009. The EFSA collated and forwarded all comments received to the Commission on 9 December 2009. At the same time the collated comments were forwarded to the rapporteur Member State for compilation in the format of a Reporting Table.

In accordance with Article 20, following consideration of the Additional Report, the comments received, and where necessary the DAR, the Commission requested thze EFSA to conduct a focussed peer review in the area of ecotoxicology abd deliver it's conclusion on myclobutanil. The conclusion from the original review was reached on the basis ogf the evaluation of the representative use of myclobutanil on apples and grapes. However the apple use was not supported in the resubmission, Terefore, t he conclusion of the peer review following the resubmission application was reached on the basis of the evaluation of the representative use as fungicide as proposed by the applicant which comprises air assisted broadcast spraying to table and wine grapes, against powdery mildew and black rot, in Northern and Southern Europe, up to a maximum 4 applications at a maximum individual application rate per spray of 48 g a.s./ha, with an interval of 10 days between applications.

It should be noted that in the resubmission dossier the use in apples against powdery mildew and scab is no longer supported.

The representative formulated product for the evaluation was 'Systhane 20 EW', an emulsion, oil in water (EW) containing 200 g/l myclobutanil.

Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection product are possible. Adequate methods are available to monitor all compounds given in the respective residue definitions for monitoring. Residues in food of plant origin can be determined with a multi-method.

In mammals, myclobutanil LD_{50} is 1600 mg/kg bw (classification as **R22** "Harmful if swallowed" is proposed). It is not toxic via dermal and inhalation routes (LD_{50} >2000 mg/kg bw and LC_{50}>5.1 mg/L). Myclobutanil is not a skin irritant or a skin sensitiser. The European Chemicals Bureau (ECB) classified myclobutanil with **R36** ("Irritating to eyes"). The primary target organ following exposure to myclobutanil is the liver. Myclobutanil induces liver enlargement accompanied by slight induction of biotransformation enzymes (in rats and mice). An overall subchronic NOAEL of 100 ppm was proposed (3.09 mg/kg bw/day). Myclobutanil does not show any genotoxic potential. In long-term studies in rat, the target organ appeared to be the testes (bilateral testicular atrophy and aspermatogenesis). The relevant NOAEL for long-term toxicity is 2.5 mg/kg bw/day from the rat study. Myclobutanil did not show any carcinogenic potential. In a two-generation rat study, myclobutanil, at a dietary concentration of 1000 ppm (80 mg/kg bw/day) produced reduced parental body weight and liver effects and decreased weight gain in pups during lactation; at slight parental toxic doses the number of females delivering litters was reduced and the incidence of still-born pups increased. The relevant parental, offspring and reproductive NOAEL is 16 mg/kg bw/day. Myclobutanil is already classified as **Repr. Cat 3, R63** ("Possible risk of harm to the unborn child"). The relevant parental NOAEL is 94 mg/kg bw/day, while the relevant developmental NOAEL is 31 mg/kg bw/day. No indication of any other neurological effects was found in the toxicological studies. The proposed **Acceptable Daily Intake** (ADI) is based on the relevant NOAEL from the long-term rat study, applying a safety factor of 100, giving an **ADI of 0.025 mg/kg bw/day**. The **Acceptable Operator Exposure Level (AOEL) of 0.03 mg/kg bw/day** was agreed to be based on the overall NOAEL (90-day and 1-year in dog) of 3.09 mg/kg bw/day, with a safety factor of 100. The rat developmental toxicity study was considered as the most appropriate to use for setting the **Acute Reference Dose (ARfD)**. An NOAEL of 31.3 mg/kg bw/day was established due to embryotoxic effects (altered viability index). Based on this NOAEL and an assessment factor of 100 the proposed **ARfD is 0.31 mg/kg bw**. There is a 300-fold margin between the proposed ARfD and the LOAEL for developmental effects in the rat developmental toxicity study. The operator and worker exposure estimates showed levels below the AOEL even when no PPE is worn (German model). The bystander exposure estimates were below the AOEL.

The metabolism of myclobutanil was investigated in grapes (representative use), apples and additionally in wheat. In grapes and apples at harvest, the major components of the residue were myclobutanil and its metabolite RH-9090 in free and conjugated form. A metabolic cleavage of the myclobutanil molecule which would generate triazole derivative metabolites was - in contrast to the wheat study - not observed in apples and grapes at the investigated pre-harvest intervals. Based on the available plant metabolism data for the categories fruit and cereals it was concluded that the metabolism is not comparable amongst different crop groups. As for the representative use, however, it was agreed that the relevant residue for the category fruit crops should be defined as myclobutanil and its metabolite RH-9090 (free and conjugated). A sufficient number of residue trials in grapes are available; however, there is still evidence required that the submitted trials fully cover the proposed residue definition and conjugates were determined with an acceptable yield. In processing studies it was investigated how the residue levels of myclobutanil and metabolite RH-9090 change when grapes are processed to juice, wine, etc. It was further demonstrated in a hydrolysis study that both myclobutanil and metabolite RH-9090 are likely to remain stable under processing conditions.

The investigation of residues in rotational and succeeding crops was considered not relevant since both apples and grapes are perennial crops that are usually not grown in rotation with other crops. However it was highlighted that upon repeated application and in the long term the issue of potential uptake of myclobutabil residues and/or triazole derivative metabolites could become relevant. The issue of triazole derivative metabolites might have to be followed up separately as this concern is not specific to the active substance myclobutanil alone but common to a number of triazole pesticides.

Moreover, the risk assessment with regard to the two isomers of myclobutanil was not addressed.

As a consequence of the identified data gaps, the consumer risk assessment for the representative use on grapes was not fully finalised.

It is also noted that the consumer could be exposed to residues of myclobutanil butyric acid,[6] which may occur in groundwater above 0.75µg/L (up to 0.81675µg/L) for which the mammalian toxicology assessment indicates the ADI for parent myclobutanil could be used. Therefore, in addition to exposure from residues in food an exposure of consumers can be expected when ground water is used as drinking water though this route of exposure is not considered significant (<1% ADI and ARfD).

In soil under aerobic conditions myclobutanil exhibits high to very high persistence, forming the minor soil metabolite myclobutanil butyric acid (accounting for a maximum of 6% of applied radioactivity (AR)) which exhibits low to moderate persistence. Mineralisation of both the chlorophenyl and triazole rings to carbon dioxide was limited and accounted for only 0.2 to 1.7% AR after 120 days. The formation of unextractable residues was a sink, accounting for 4 to 16% AR after 120 days. Myclobutanil exhibits medium to low mobility in soil, myclobutanil butyric acid exhibits very high mobility in soil. There was no indication that adsorption of either myclobutanil or myclobutanil butyric acid was affected significantly by differing soil pH. Data on degradation in soil under anaerobic conditions are not available and it was considered they will be necessary to support the applied for use on apples in some territories of the EU.

In dark natural sediment water systems myclobutanil partitioned from the water column to sediment where it exhibited very high persistence. The terminal metabolite, CO_2, accounted for a maximum of 0.3% AR at 105 days (study end). Unextracted sediment residues were a sink but represented only 4.3 to 9.8% AR at study end. The necessary surface water and sediment exposure assessments were appropriately carried out using the agreed FOCUS scenarios approach for myclobutanil at steps 3 and 4, with spray drift mitigation being applied at step 4. These values are the basis for the risk assessment discussed in this conclusion.

[6] myclobutanil butyric acid: (3*RS*) 3-(4-chlorophenyl)-3-cyano-4-(1*H*-1,2,4-triazol-1-yl)butanoic acid

On the basis of the available information, it can be concluded that for the representative use assessed on grapes, groundwater exposure by myclobutanil above the parametric drinking water limit of 0.1 µg/L, will not occur in geoclimatic situations represented by 6 out of the 7 pertinent FOCUS groundwater scenarios. In geoclimatic situations represented by just the Piacenza scenario, groundwater exposure might occur with concentrations (annual average recharge leaving the top 1m soil layer) estimated to be 0.21 µg/L. For the metabolite myclobutanil butyric acid, groundwater exposure above the parametric drinking water is expected in geoclimatic situations represented all 7 pertinent FOCUS groundwater scenarios. In geoclimatic situations represented the FOCUS Hamburg vine groundwater scenario concentrations > 0.75 µg/L (a key assessment trigger from the groundwater metabolite relevance guidance document) might be expected. A groundwater metabolite non-relevance assessment was therefore necessary for myclobutanil butyric acid. An assessment following the relevant guidance was available that demonstrated non-relevance.

The risk to birds, mammals, aquatic organisms, bees, non-target arthropods, earthworms, other soil non-target macro-organisms, soil non-target micro-organisms, non-target plants and biological methods of sewage treatment was assessed as low for the respresentative use in grapes. It was identified that the risk assessment did not address the potential for different myclobutanil isomer ratios to be present in the environment.

KEY WORDS

myclobutanil, peer review, risk assessment, pesticide, fungicide

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BACKGROUND

Commission Regulation (EC) No 1490/2002[7], as amended by Commission Regulation (EC) No 1095/2007[8]lays down the detailed rules for the implementation of the third stage of the work programme referred to in Article 8(2) of Council Directive 91/414/EEC[9]. This regulates for the European Food Safety Authority (EFSA) the procedure for organising, upon request of the Commission of the European Communities (hereafter referred to as 'the Commission'), a peer review of the initial evaluation, i.e. the Draft Assessment Report (DAR), provided by the designated rapporteur Member State. Myclobutanil is one of the 79 substances of the third stage, part A of the review programme covered by the Regulation (EC) No 1490/2002, as amended by Commission Regulation (EC) No 1095/2007 designating Belgium as rapporteur Member State.

In accordance with the provisions of Article 10(1) of the Regulation (EC) No 1490/2002, Belgium submitted the report of its initial evaluation of the dossier on myclobutanil, hereafter referred to as the draft assessment report, to the EFSA on 4 July 2005. Following an administrative evaluation, the EFSA communicated to the rapporteur Member State some comments regarding the format and/or recommendations for editorial revisions and the rapporteur Member State submitted a revised version of the draft assessment report. In accordance with Article 11(2) of the Regulation (EC) No 1490/2002 the revised version of the draft assessment report was distributed for consultation on 29 March 2006 to the Member States and the main applicant Dow AgroSciences as identified by the rapporteur Member State.

The comments received on the draft assessment report were evaluated and addressed by the rapporteur Member State. Based on this evaluation, representatives from Member States identified and agreed during a written procedure in October – November 2006 on data requirements to be addressed by the notifier as well as issues for further detailed discussion at expert level.

Taking into account the information received from the notifier addressing the request for further data, a scientific discussion of the identified data requirements and/or issues took place in expert meetings in March 2007. The reports of these meetings have been made available to the Member States electronically.

A discussion of the outcome of the consultation of experts took place with representatives from Member States on 14 November 2007 leading to the conclusions set out in the EFSA conclusion finalised on 4 June 2009 (EFSA scientific Report 2009 (298)).

Following the Commission Decision of 5 December 2008 (2008/934/EC)[10] concerning the non-inclusion of myclobutanil in Annex I to Council Directive 91/414/EEC and the withdrawal of authorisations for plant protection products containing that substance, the applicant Dow AgroScience made a resubmission application for the inclusion of myclobutanil in Annex I in accordance with the provisions laid down in Chapter III of Commission Regulation (EC) No. 33/2008[11]. The resubmission dossier included further data in all section.

In accordance with Article 18 of Commission Regulation (EC) No. 33/2008, Belgium, being the designated rapporteur Member State, submitted an evaluation of the additional data on myclobutanil in the format of an Additional Report (Belgium, 2009). The Additional Report was received by the EFSA on 22 October 2009.

[7] OJ L224, 21.08.2002, p.25
[8] OJ L246, 21.9.2007, p.19

[10] OJ No L 295, 04.11.2008, p.53
[11] OJ No L 295, 04.11.2008, p.53

In accordance with Article 19, the EFSA distributed the Additional Report to the Member States and the applicant for comments on 26 October 2009. In addition the EFSAA conducted a public consultation on the additional report- The EFSA collated and forwarded all comments received to the Commission on 9 December 2009. At the same time, the collated comments were forwarded to the RMS for compilation in the format of a Reporting Table. The applicant was invited to respond to the comments in column 3 of the Reporting Table. The comments and the applicant's response were evaluated by the RMS in column 3.

The scope of the peer review and the necessity for additional information, not concerning new studies, to be submitted by the applicant in accordance with Article 20(2), was considered in a telephone conference between the EFSA, the RMS, and the Commission on 25 January 2010; the applicant was also invited to give its view on the need for additional information and additional information was requested in the sections of fate and behaviour and ecotoxicology. On the basis of the comments received, the applicant's response to the comments, and the RMS' subsequent evaluation thereof, it was concluded that EFSA should organise a consultation with Member State experts in the section of ecotoxicology and that additional information should be requested from the applicant in the area of fate and behaviour.

The outcome of the telephone conference, together with EFSA's further consideration of the comments is reflected in the conclusions set out in column 4 of the Reporting Table. All points that were identified as unresolved at the end of the comment evaluation phase and which required further consideration , including those issues to be considered in consultation with Member State experts, and the additional information to be submitted by the applicant, were compiled by the EFSA in the format of an Evaluation Table.

The conclusions arising from the consideration by the EFSA, and as appropriate by the RMS, of the points identified in the Evaluation Table were reported in the final column of the Evaluation Table.

A final consultation on the conclusions arising from the peer review of the risk assessment took place with Member States via a written procedure in June 2010.

This conclusion report summarises the outcome of the peer review of the risk assessment on the active substance and the representative formulation evaluated on the basis of the evaluation of the representative use as a fungicide on grapes as proposed by the applicant. A list of the relevant end points for the active substance as well as the formulation is provided in Appendix A. In addition, a key supporting document to this conclusion is the Peer Review Report, which is a compilation of the documentation developed to evaluate and address all issues raised in the peer review, from the initial commenting phase to the conclusion (EFSA 2010). The Peer Review Report comprises the following documents:

- the comments received on the additional report
- the resulting reporting table (rev. 1-1 of 25 January 2010)

as well as the documents summarising the follow-up of the issues identified as finalised at the end of the commenting period:

- the reports of the scientific expert consultation;
- the evaluation table (07 July 2010)).

Given the importance of the additional report including its addendum (Belgium 2010; compiled version of July 2010 containing all individually submitted addenda) and the peer review report with respect to the examination of the active substance, both documents are considered respectively as background documents A and B to this conclusion. The documents of the peer review report and the final addendum developed and prepared during the course of the initial review process are made

publicly available as part of the back ground documentation to the original conclusion finalised on 4 June 2009 (EFSA 2009).

THE ACTIVE SUBSTANCE AND THE FORMULATED PRODUCT

Myclobutanil is the ISO common name for (*RS*)-2-(4-chlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)hexanenitrile (IUPAC).

Myclobutanil belongs to the class of conazole fungicides. Myclobutanil is a systemic fungicide with preventive, curative and eradicant properties. It is a sterol biosynthesis inhibitor, inhibiting primarily the C-14-demethylation step in the fungal sterol biosysnthesis pathway. The active substance is absorbed by the leaves and stems and is transported upward in the plant into areas of new growth via the xylem.

The representative formulated product for the evaluation was 'Systhane 20 EW', an emulsion, oil in water (EW) containing 200 g/l myclobutanil, registered under different trade names in Europe.

The representative uses evaluated in the resubmission comprise foliar spraying against powdery mildew (*Uncinula necator)*, and black rot *(Guignardia bidwelli)* in table and wine grapes, in all EU countries, up to a maximum four applications at a maximum individual application rate per spray of 48 g a.s./ha, with an interval of 10 days between applications.

It should be noted that in the resubmission dossier the use in apples is no longer supported.

CONCLUSIONS OF THE EVALUATION

1. Identity, physical/chemical/technical properties and methods of analysis

The minimum purity of myclobutanil technical material is 925 g/kg. The technical material is a racemic mixture (1:1). No FAO specifications exist.

The assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the identity, physical, chemical and technical properties of myclobutanil or the respective formulation. The main data regarding the identity of myclobutanil and its physical and chemical properties are given in Appendix A.

Adequate analytical methods are available for the determination of myclobutanil in the technical material and in the representative formulation as well as for the determination of the respective impurities in the technical material. The rapporteur Member State identified 1-methylpyrrolidin-2-one as a relevant impurity in the technical active substance, however the experts of the PRAPeR 16 meeting concluded that the determination of the relevant impurity in the formulation is not required as the it would not be formed during the manufacturing process of the formulation or during storage.

Sufficient test methods and data relating to physical, chemical and technical properties and analytical methods are available to ensure that quality control measurements of the plant protection product are possible.

The multi-method EN 15662:2008 (QuEChERS) is suitable as an enforcement method for the determination of residues of myclobutanil in matrices of plant origin (acidic matrices) with a LOQ of 0.025 mg/kg.

Currently it is not deemed necessary to define a residue or propose MRLs for food of animal origin, however the German multi-residue method DFG S19 (extended revision) using GC-ECD allows the determination of metabolite RH-9090 in matrices of animal origin (milk, meat, liver and kidney) with LOQs of 0.01 mg/kg.

Residues of myclobutanil in soil can be determined with the German multi-residue enforcement method DFG S19 using GC-ECD with a LOQ of 0.05 mg/kg.

LC-MS-MS methods are available for the determination of residues of myclobutanil in water (drinking water, groundwater, surface water) with LOQs of 0.05 µg/l and in air with a LOQ of 0.7 µg/m³.

Analytical methods for residues for body fluids and tissues are not required since myclobutanil is not classified as toxic or very toxic.

Adequate methods are available to monitor all compounds given in the respective residue definitions where these have been finalised, i.e. myclobutanil in food of plant origin (grapes), in soil, water and in air.

2. Mammalian toxicity

Myclobutanil was discussed in a meeting of experts (PRAPeR 19) in March 2007. Myclobutanil tested in toxicological studies was a racemic mixture. A general data gap was identified during the meeting: the information on the comparability of the toxicological studies performed with technical material of different purities was missing, as well as toxicological information on impurities. The point on the issue was still open after the meeting.

The applicant was requested to provide a case and/or data to show that the increased levels of two impurities (3 and 8) will not have a significant adverse effect on the toxicity of technical myclobutanil. Both impurities are present in the 'old' batches, as well as in the 'new' batches. Their amounts are increased. The rapporteur Member State considered that their increase is not of toxicological concern.

From the confidential part of the DAR it is evident that the increase of the impurities was reported for the technical specification of a purity of 92.5% compared to the batches with a lower purity. So far the meeting only considered the "old" batches with a lower purity, which varies from 79 to 93%.

The purity of the batches used in the new acute toxicity studies is 95.7%. No information is available on the impact of the impurities with regard to the toxicological parameters.

The RMS identified 1-methylpyrrolidin-2-one as a relevant impurity in the technical active substance.

During the resubmission, the RMS submitted a revised vol. 4 with a new assessment of the impurities 3 and 8: the RMS considered that the amount of the 2 impurities in the proposed specification is quite similar to the amount theoretically acceptable, in the assumption that they are not toxicologically relevant. The assumption of non-toxicological relevance was based on a QSAR analysis, which revealed no alerts. In the applicant's and RMS' opinion the differences of impurity levels between the new source and old source would suggest that if the increase were to be of toxicological concern the impurities would have showed alerts that would be picked up in the QSAR models run. EFSA notes that the QSAR approach is not fully validated and acceptable for this purpose and that although a different pattern of toxicity between the new and old batches is unlikely however this could not be proven. The data gap therefore remains open.

2.1 Absorption, Distribution, Excretion and Metabolism (Toxicokinetics)

In rats and mice, myclobutanil is rapidly absorbed; comparing urinary excretion after oral and intravenous administration of a single low dose suggests that bioavailability is important in rats, reaching 100%. Therefore, no correction for oral absorption is required. Myclobutanil is widely distributed with high levels detected in liver, kidney, adrealsand intestine. No significant accumulation was seen after 96 hours from administration.

Metabolism is extensive; low levels of unchanged parent compound are detected in urine and faeces. There is no cleavage of the molecule and the major metabolic pathway involves oxidation of the butyl side chain. Most of an oral dose is eliminated in urine and faeces within 24 to 48 hours.

2.2 Acute toxicity

Myclobutanil LD_{50} is 1600 mg/kg bw. Classification as R22 "Harmful if swallowed" was proposed. It is not toxic via dermal and inhalation routes (LD_{50} > 2000 mg/kg bw and LC_{50} > 5.1 mg/L 4 h, nose only, highest obtainable concentration).

Myclobutanil is not a skin irritant or a skin sensitiser. The need of classification R36 "Irritating to eyes" was discussed in the experts' meeting. Based on the information available classification would not be necessary. However, it was noted that the European Chemicals Bureau (ECB) had already classified the substance with R36.

The applicant submitted a new acute toxicity package, available in the experts' meeting. Compared with the previous source the new source has a different level of purity. It was unclear whether the manufacturing process was changed. The results of the acute studies show lower toxicity. It was not clear whether the effects are related to the substance itself or the impurities. The previous source was proposed to be classified with Xn; R22, which does not apply any longer to the new source.

The meeting decided to consider only the 'old' source with the lower purity. Evidence of comparability between the old and the new sources has to be proven to have the new submitted studies considered. Therefore a data gap was proposed: information on the comparability of the toxicological studies performed with technical material of different purity is required, as well as toxicological information on impurities.

2.3 Short-term toxicity

The primary target organ following exposure to myclobutanil is the liver. Myclobutanil induces liver weight increase associated with hepatocellular hypertrophy in rats, mice and dogs. Liver enlargement is accompanied by slight induction of biotransformation enzymes (in rats and mice only). Rats and mice appeared to be of comparable sensitivity towards myclobutanil. In the 90-day rat study, hepatocellular necrosis was evident at high doses. The relevance of liver effects in dogs (90-day and 1-year study) was discussed during the meeting. The two studies have been performed with different batches with different levels of purity. The liver weight increases were between 9 and 52%. In the 90-day dog study the liver enzymes are not affected up to 1600 ppm although the liver weight increased. In both studies reduced body weight gain and decrease of food intake were observed at the highest dose levels (1600 ppm).

Taking into account the increased organ weight together with histological alterations (hepatocyte hypertrophy) at the level of 200 ppm in the 90-day dog study, the meeting proposed to set the NOAEL at 10 ppm for the 90-day dog study and a NOAEL of 100 ppm for the 1-year dog study. An overall subchronic NOAEL of 100 ppm was proposed (corresponding to 3.09 mg/kg bw/day).

Skin irritation and/or gross and microscopic changes of the treated skin were observed after application of myclobutanil formulations at 100 mg/kg bw/day. The NOAEL for local effects is 10 mg/kg bw/day, whereas no systemic toxic effects were reported (NOAEL systemic toxicity 100 mg/kg bw/day).

2.4 Genotoxicity

Myclobutanil did not show any genotoxic potential in both *in vitro* and *in vivo* genotoxicity tests.

2.5 Long-term toxicity

In male rats an increased incidence of testicular atrophy occurred bilaterally. These effects appeared clearly at the 12-month sacrifice. There was no increased incidence of neoplastic findings in any of the organs of treated animals. Liver changes consisted of minimal to moderate centrilobular to midzonal hepatocellular enlargement and vacuolisation. Bilateral aspermatogenesis occurred and was

accompanied by hypospermia and cellular debris in the epididymides. In mice, liver effects consisted of hepatocellular necrosis, foci of altered hepatocytes and hepatocellular vacuolation.

The relevant NOAEL for long-term toxicity is 2.5 mg/kg bw/day from the rat study. Myclobutanil did not show any carcinogenic potential.

2.6 Reproductive toxicity

In a two-generation rat study, myclobutanil produced reduced parental body weight and liver effects and decreased weight gain in pups during lactation. Atslight parental toxic doses the number of females delivering litters was reduced and the incidence of still-born pups increased. In the meeting it was discussed whether the results, observed at high dose levels, justify classification with R62. Findings in the testes at the highest dose tested may be linked to aromatase inhibition. A decreased number of females delivering litters was also observed at the highest dose level tested. Systemic toxicity was observed at 200 ppm. The meeting agreed that these findings do not warrant the classification with R62. The relevant parental, offspring and reproductive NOAEL is 16 mg/kg bw/day.

A developmental rat study was conducted at doses ranging from 31 to 469 mg/kg bw/day. Fertility of females was not affected. Clinical signs of toxicity were observed in dams at 312 and 469 mg/kg bw/day. Viability index of foetuses was reduced at 93 mg/kg bw/day onwards with a concomitant increase in resorptions per litter and litters with more than 2 resorptions. It was noted that myclobutanil is already classified as Repr. Cat 3., R63 (“Possible risk of harm to the unborn child”). The relevant parental NOAEL is 94 mg/kg bw/day, while the relevant developmental NOAEL is 31 mg/kg bw/day.

2.7 Neurotoxicity

Myclobutanil does not have any potential to cause delayed neurotoxicity. Hence, no test of delayed neurotoxicity was required and none have been conducted. No indication of any other neurological effects was found in the toxicological studies.

2.8 Further studies

An oral acute toxicity study was carried out on two main metabolites of myclobutanil in plants (RH-9090 and RH-9089) and on two impurities in myclobutanil. The most important metabolic route in plants is via production of RH-9090, which can further be transformed to RH-9089. Both metabolites were major metabolites in the rat.

The relevance of metabolites RH-9090 and RH-9089 was discussed in the meeting. The metabolites RH-9090 and RH-9089 are major rat metabolites (>10%). The meeting agreed on the relevance, because of the parent toxicological properties. Their equivalent toxicity is not proven but it can be presumed they are in the same range of toxicity.

It was discussed whether the toxicity observed is more related to the metabolites or related to myclobutanil. Information on the amounts of metabolites occurring in the residues is needed and therefore confirmation from the PRAPeR experts’ meeting on residues was required. The meeting on residues presented information about the residue levels. The rapporteur Member State considered that toxicological studies performed with the parent compound cover the toxicity of both metabolites. Taking into account the estimated consumer exposure via the residues in relation to their amount in the rat metabolism it was agreed that they do not pose any concern.

Acute oral toxicity of myclobutanil metabolites in plants and impurity RH-8812 was comparable to that of myclobutanil. RH-8813 was not classified for acute oral toxicity.

Myclobutanil butyric acid exceeds 0.1µg/L in vulnerable groundwater aquifers (with concentrations exceeding 0.75µg/L, but at just the single Hamburg scenario, see section 4.2.2). In the DAR, no

toxicological information or assessment was available. During the resubmission new toxicological studies were summarised (*in vitro* and *in vivo* genotoxicity studies, overall showing no genotoxic potential, and a developmental toxicity study, with maternal and developmental NOAELs>450mg/kg bw/day). In addition, the assessment of the relevance of this metabolite in groundwater in accordance with the Guidance Document SANCO/221/2000 –rev10 was summarised, showing its non relevance. On the basis of the available data it is not possible to derive specific reference values for myclobutanil butyric acid therefore the reference values for myclobutanil can be applied to the metabolite as well, if needed.

2.9 Medical data

The available medical surveillance data on manufacturing plant personnel working with myclobutanil, show no abnormalities to suggest adverse effects on health.

Clinical cases and poisoning incidents have shown a range of symptoms common to chemical poisoning events, which include irritation of skin, eyes, nose or throat, nasal congestion, headaches, nausea and vomiting.

2.10 Acceptable daily intake (ADI), acceptable operator exposure level (AOEL) and acute reference dose (ARfD)

Acceptable daily intake (ADI)

The proposed ADI is based on the relevant NOAEL derived from the long-term rat study (NOAEL 2.5 mg/kg bw/day). An assessment factor of 100 was applied, giving an ADI of 0.025 mg/kg bw/day.

Acceptable operator exposure level (AOEL)

In the experts' meeting the AOEL was discussed. It was agreed to base it on the overall NOAEL (90-day and 1-year dog) of 3.09 mg/kg bw/day, resulting in an AOEL of 0.03 mg/kg bw/day with a safety factor of 100.

Acute reference dose (ARfD)

The rat developmental toxicity study was considered as the most appropriate to use for setting the ARfD. A NOAEL of 31.3 mg/kg bw/day was established in this study due to embryotoxic effects (altered viability index). Based on this NOAEL and an assessment factor of 100 the proposed ARfD is 0.31 mg/kg bw. There is a 300-fold margin between the proposed ARfD and the LOAEL for developmental effects in the rat developmental toxicity study. The experts agreed on the value.

2.11 Dermal absorption

The dermal absorption values proposed in the DAR for 'Systhane 20 EW' were 18% for the concentrate and 30% for the dilution. A new *in vitro* study with rat and human skin was submitted and the results were presented in an addendum to the DAR. A correction factor was not necessary for the concentrate, but for the dilution a correction factor of 2.7 was established. A recalculation of the values has been done during the meeting because the faecal excretion has not been considered in the first calculation. The revised values are 25% for the concentrate and 15% for the dilution.

2.12 Exposure to operators, workers and bystanders

The potential operator exposure was estimated for the intended use of 'Systhane 20 EW', an emulsion (oil in water) formulation containing 200 g/L myclobutanil. In the initial review uses on alle and grape were evaluated, however in the resubmission the use on apple was no longer supported.

It was highlighted by the meeting on physical-chemical properties that the racemic mixture consists of two possible optic isomers in the ratio 50:50. This was not specifically considered by the mammalian toxicology meeting. The experts agreed that provided the racemic mixture is stable then this concern is

covered by the toxicological tests performed. To this aim a data gap was set after the PRAPeR experts meeting to address the impact of different isomer ratios on the exposure assessment of myclobutanil for operators, workers and bystanders.

During the resubmission phase, the applicant provided some arguments with regard to the possible different toxicity of the different isomers of myclobutanil. According to the applicant the two optical isomers would exhibit equivalent efficacy as they show similar inhibition of 14a-demethylase in fungal systems, therefore the structurally similar mammalian enzymes would also be equally affected by the two optical isomers. However, no further toxicological and mechanistic data were provided to address this issue and the data gap remains open.

Operator exposure

Applying a dermal absorption factor of 25% for the concentrate and 15% for the diluted formulation, and considering the AOEL established during the experts' meeting, the rapporteur Member State was asked to perform new calculations for operator, worker and bystander exposure (submitted in the addendum March 2007 and reported below).

Operator exposure estimates

	% of AOEL	
	No PPE	**PPE**
UK POEM model		
Grapes, orchard	77%	---
Apples, orchard	39%	---
GERMAN MODEL		
Grapes, orchard	74%	---
Apples, orchard	80%	---

The operator exposure estimates showed levels below the AOEL of 0.03 mg/kg bw/day even when no PPE is worn.

During the commenting phase on the EFSA draft conclusion and during the evaluation meeting held in Parma on 14 and 15 November 2007, some inaccuracies have been highlighted for operator and worker exposure estimates (e.g. the re-calculations provided by the rapporteur Member State have been performed considering, for both UK POEM and German model, a treated area of 8 ha, which is not the standard proposed by the UK POEM. This would lead to an underestimation of the operator exposure). Therefore, after the meeting it was decided to revise calculations in order to provide the correct assessment. It is noted that re-calculations presented in the EFSA addendum does not change the final conclusion on the risk assessment, with regard to the safety of intended uses. The EFSA addendum is not peer reviewed.

The correct figures are as follows

Crop/application method	% of AOEL	
	No PPE worn	PPE
UK POEM model		
Grapes, orchard	160%	54.8% (gloves during M/L)
Apples, orchard	286%	75.1% (gloves during M/L and application)
GERMAN MODEL		
Grapes, orchard	42%	-
Apples, orchard	80%	-

Conclusions: the estimated exposure levels for the operator are below the AOEL, without the use of PPE for the German model and with the use of PPE for the UK POEM.

Worker exposure

According to the rapporteur Member State the exposure of workers re-entering the field treated with 'Systhane 20 EW' was estimated to be 32% of the AOEL (Poppendorf, 1992).

In the Evaluation meeting it was noted that the refinement has not considered new parameters properly (in particular, the maximum dislodgeable foliar residue (DFR) has not been calculated according to the relevant application rate). However, even applying the correct DFR, the estimated exposure for the highest application rate (apples) represents the 61.7% of the AOEL (see EFSA addendum). It is noted the only the exposure occurring after 1 single application has been estimated.

Bystander exposure

Bystander exposure was considered to be brief and incidental, and estimated to be less than 1% of the AOEL. In the evaluation meeting, the UK reiterated that calculating bystander exposure according to the study by Lloyd et al. (1987) instead of Lloyd et al. (1983) would have provided a more precise figure.

3. Residues

Myclobutanil was discussed in the meeting of experts in Parma in March 2007 (PRAPeR 20, Round 4). Two addenda to the DAR were submitted. Of these, only the addendum of March 2007 was peer reviewed in 2007.

In the peer review of the resubmission the assessment for the original representative use on apples was not updated as this use was no longer supported by the applicant in their resubmission application for Annex 1 listing. Therefore data gaps that relate to the use on apples are not included in Appendix A or considered in the sections of this conclusion regarding: the list of studies to be generated, assessments not finalised or critical areas of concern.

It is noted that myclobutanil consists of two optical isomers (enantiomers). It should also be noted that the methods of analysis used in all the residue studies were not stereoselective. Thus the regulatory dossier provides no information on the behaviour of each individual myclobutanil enantiomer in plants and livestock. Therefore all residues reported as myclobutanil in this conclusion are for the sum of the two enantiomers. It is not known if either isomer is metabolised or degraded more quickly than the other in the matrices studied.

3.1 Nature and magnitude of residues in plant

3.1.1. Primary crops

The metabolism of myclobutanil was investigated in grapes, apples (category fruit) and wheat (cereals) with myclobutanil ^{14}C-labelled in either the phenyl or triazole ring of the molecule. The notified representative uses originally applied for were on grapes and apples; for the resubmission application only the use in grapes was supported. Foliar application was made at a rate equivalent to the GAP supported for grapes, or exaggerated (6.7 N) in terms of the GAP initially supported for apples. The PHI in the grape was shorter than the minimum PHI defined in the GAP while in the apple study the PHI was equivalent to GAP conditions.

In grapes and apples at harvest, the major components of the total radioactive residues (TRR) were parent myclobutanil (66% in grapes, 49% in apple), and the non conjugated and conjugated alcohol metabolite RH-9090 (together 15% in grapes and 35% in apple). A considerable amount of myclobutanil was recovered on/in the peel of the fruits as reflected by the results for the analysed pomace (72% in grape pomace, 56% in apple pomace). In contrast, in apple and grape juice the level of metabolite RH-9090 (including sugar conjugate) was increased (47% in grape juice, 68% in apple juice) when compared to the myclobutanil levels determined (26 to 33% in grape juice, 22 to 24% in apple juice). In both apple and grape the metabolite RH-9089 was detected as a minor metabolite (up to 4% TRR). No other metabolites were identified. The rate of identification of metabolites was considered satisfactory. No significant difference between the two labels with regard to the metabolite pattern was found.

Based on the results of the metabolism studies in apples and grapes it has been proposed that the metabolic pathway of myclobutanil in fruit proceeds mainly via the non-aromatic hydroxylation of the side-chain of myclobutanil to form the alcohol RH-9090. This metabolite is either further conjugated with sugar (glucoside, malonyl glucoside) or reduced to form the ketone RH-9089. None of the metabolites formed in apples and grapes were of particular toxicological concern as they were also found in rat metabolism.

Another route of degradation of myclobutanil seems to occur in cereals (wheat); however wheat is not a representative use. In addition to myclobutanil and metabolite RH-9090, present in important amounts in wheat grain and straw were triazolyl alanine and triazolyl acetic acid. This indicated a metabolic cleavage of myclobutanil at the phenethyl triazole linkage which lead to generation of the metabolite triazolyl alanine with further degradation to the metabolite triazolyl acetic acid. These metabolites are not specific to myclobutanil but to all triazole pesticides.

With regard to the triazole derivative metabolites: 1,2,4-triazole, triazole alanine and triazole acetic acid, the PRAPeR meeting of experts in toxicology (PRAPeR 14) in January 2007 concluded that toxicological end points and reference values should be adopted as a result of their effect on reproduction and development.

Based on the myclobutanil metabolism studies available on the fruits and cereals categories, it is concluded that the metabolism is not comparable between the two crop groups. Specifically, triazole derivate metabolites were found in the wheat metabolism study, while triazole derivate metabolites were not found in the apples and grapes metabolism studies.

The experts in the meeting PRAPeR 20 agreed that a general residue definition covering all crops categories can not be proposed based on the available data. It was concluded that, if in the future new uses other than fruits and cereals will be envisaged, new metabolism studies might be necessary to particularly address potential occurrence of triazole derivate metabolites in those crops.

As metabolism studies are available for grapes and apples, it is considered that the broad category of fruit crop is sufficiently covered. Therefore, the residue definition has been proposed as:

myclobutanil, metabolite RH-9090 free and conjugated expressed as myclobutanil for risk assessment and,
myclobutanil alone for monitoring purposes.

The proposed definitions should be limited to the fruit crop category. A conversion factor could not be concluded as further clarification with regard to the analysed residue in the submitted residue trials is necessary (see next paragraphs).

Although the critical GAP for both apples and grapes defines four applications, the older sets of the submitted residue trials in apple and grapes from Northern and Southern Europe (seasons 1986, 1996/97) were conducted using higher numbers of applications (6 to 12).

As it is agreed that the last application prior to harvest is the most critical in terms of the residue level in the harvested crop, it is expected that additional early season application prior to formation of the fruit would not contribute significantly to the residue level present at harvest from the four last applications at the end of the season. Therefore the submitted residue trials with a higher number of applications were considered to support the critical GAP. In addition more recent residue trials (2004) including also trials with four applications were submitted to supplement the trials with a higher application rate and to compare the results of the different sets of trials.

Myclobutanil and the metabolite RH-9090 are the residues analysed in the trials. All results are supported by acceptable storage stability data. However, the applicant should provide evidence that the submitted trials cover the residue definition, in particular with regard to conjugates. It should be demonstrated that the method used would extract all the conjugates and that the hydrolysis step in the method gives an acceptable yield. With the resubmission application the issue of whether conjugates were determined with an acceptable yield in the residue trials could not be clarified, and the data gap remained.

A study investigating the behaviour of myclobutanil and metabolite RH-9090 when simulating representative processing conditions indicated that both compounds can be regarded as stable. Also studies on the effects of processing on the residue levels are available in apples and grapes. In these studies myclobutanil and RH-9090 residues were analysed in grape juice and wine and in apple juice, purée, cooked apple and pomace. A concentration of residues was found in apple pomace.

No data was submitted on processing of grapes to raisins.

3.1.2. Succeeding and rotational crops

Even though myclobutanil is highly to very highly persistent in soil (refer to section 4.1), the investigation of residues in succeeding crops was considered not relevant since both apples and grapes are perennial crops that are usually not grown in rotation with other crops. Any potential residue taken up from soil should most likely be myclobutanil. It is however unclear whether a continuous use of myclobutanil on grapes may have an impact on the final residue levels in grapes.

The formed soil metabolite myclobutanil butyric acid was present only at low levels in soil and is therefore not considered a residue of concern for fruit crops. In year long laboratory soil incubation studies (see section 4.1.1) 1,2,4-triazole was not formed in the soil at levels that required identification according to current guidance in the section of fate and behaviour, but it cannot be excluded that it will be formed long term from continuous use of this compound and there may be uptake of this compound and or other 1,2,4-triazole derivatives. This issue of triazole metabolites concerns a number of active substances and will need to be followed up separately in the future.

3.2. Nature and magnitude of residues in livestock

For the notified use in grapes with the resubmission application the assessment of residues in livestock is no longer relevant.

In a previous review procedure livestock exposure from the initially notified use in apples was considered. Significant exposure of livestock to residues in feed may occur when fruit pomace is used in livestock diet, in particular in ruminant diet. Therefore, in a study with dairy cattle a mixture of myclobutanil and the two metabolites RH-9090 and RH-9089 was administered to lactating cows in order to reflect a possible exposure of ruminants to residues from treated crops. However, the ratio of compounds in the applied testing material does not reflect that occurring in fruit pomace, but it could be accepted as to the aim of a metabolism study. Myclobutanil was labelled on the phenyl ring and the metabolites were labelled on the triazole ring. The identification rate of residues was generally low (circa 50% in milk, circa 30% in liver, circa 40% in kidney; no identification in muscle and fat due to the low level of total residues). The majority of the experts in the PRAPeR 20 meeting agreed that the level of identification was insufficient and a robust residue definition for risk assessment and monitoring could not be concluded on the basis of the available data. Therefore, a new data gap was identified with regard to a ruminant metabolism study where the compound is labelled on both rings. Other points previously identified for discussion by experts have no longer been considered in the meeting since a new ruminant metabolism study is required.

Currently a residue definition in ruminant products can not be proposed.

It is noted that after the meeting of experts the rapporteur Member State indicated in a letter to EFSA (13 June 2007) their disagreement with the identified data gap for a ruminant metabolism study.

It is noted that for the sole representative use in grapes in the resubmission application this data gap is not applicable.

There was also a feeding study in cows with myclobutanil submitted. In this feeding study one of the compounds tested was the diol RH-0294[12] (erroneously referred to in the DAR as carboxylic acid). The relevance of this feeding study for the residues assessment can only be decided when an animal residue definition is concluded.

Apple and grapes products are not relevant feeding stuffs in poultry diet. Even though not required to support the representative uses, a study in laying hens was submitted and evaluated in the DAR. From a qualitative point of view, the metabolism in poultry is considered sufficiently investigated. Myclobutanil and two metabolites (RH-9090 and RH-9089) are likely to be the predominant components of the residue. Any contribution from triazole metabolites in the poultry diet will need to be considered in addition, if relevant for future uses.

With regard to the notified representative uses the experts at the meeting concluded that due to the data gap for the ruminant metabolism study a restriction could be proposed that fruit pomace from treated crops must not be fed to animals. For the sole representative use in grapes in the resubmission application the initially proposed restriction is no longer applicable.

3.3. Consumer risk assessment

Currently the consumer risk assessment with regard to the notified representative use on grapes cannot be finalised due to missing data and information. The consumer risk assessment that has provisionally been conducted by the rapporteur Member State with the EFSA PRIMo rev. 2 indicated the consumer intake of myclobutanil and metabolite RH-9090 from a use in grapes was 16% of the ADI and 21 % of the ARfD respectively. This provisional consumer risk assessment is characterised by a number of uncertainties.

- It is not confirmed whether the available residue data cover all compounds of the residue definition for risk assessment i.e. do fully include the conjugated form of metabolite RH-9090.

Insufficient information to address the issue has been made available in the resubmission dossier.

- Moreover, the nature of the final residue in plant (and animal commodities- only relevant for the use in apples no longer supported) was not studied with regard to the two isomers of myclobutanil. Thus it is not known if either isomer is metabolised or degraded more quickly and to which ratio of isomers consumers and livestock may be exposed. The experts in PRAPeR 20 agreed that the applicant should address the consumer risk assessment with regard to the two the isomers of myclobutanil. Insufficient information to address the issue has been made available in the resubmission dossier.

- Information as to whether significant uptake of myclobutanil into the crop (grapes) can be expected in following growing seasons and upon continuous use of myclobutanil and may have an impact on the final residue levels is not available.

- Finally, the exposure and risk assessment does currently not consider the issue of triazole derivative metabolites. It was highlighted that in the long term, the issue of potential uptake of triazole derivative metabolites in crops in the vineyard could become relevant. The issue of triazole derivative metabolites might be followed up separately as this concern is not specific to the active substance myclobutanil alone but to a number of triazole pesticides. Yet, the issue is considered pertinent in the risk assessment of uses of the individual active substances.

Despite the identified uncertainties and as mentioned by the RMS, the margin of safety seems sufficient to exclude a risk to the consumer from the use of myclobutanil in grapes. Data gaps need however to be addressed in order to finalise the risk assessment and to confirm that the toxicological reference values are effectively not exceeded.

It is also noted that the myclobutanil butyric acid metabolite may leach to ground water at significant levels (refer to section 4.2.2) The 0.1µg/L trigger was exceeded in all the pertinent FOCUS grapevine scenarios with a concentration of >0.75 µg/L (0.816µg/L) being estimated for the FOCUS Hamburg grapevine scenario. Therefore, an additional exposure of consumers can be expected when ground water is used as drinking water though this route of exposure is not considered significant (<1% ADI and ARfD).

3.4. Proposed MRLs

The proposed EU MRLs for table/wine grapes is 1 mg/kg.

4. Environmental fate and behaviour

Myclobutanil was discussed at the PRAPeR experts' meeting for environmental fate and behaviour in March 2007 (PRAPeR 17). The fate and behaviour characteristics of the potential very minor soil metabolite 1,2,4-triazole (not identified in the available studies; a metabolite with the potential to be formed by several triazole moiety containing active substances) was discussed at the PRAPeR experts' meeting for environmental fate and behaviour in January 2007 (PRAPeR 12). It should also be noted that the methods of analysis used in all the fate and behaviour studies were not stereoselective. Therefore the regulatory dossier provides no information on the behaviour of each individual myclobutanil enantiomer in the environment. Therefore all residues reported as myclobutanil in this conclusion are for the sum of the two enantiomers. It is not known if either isomer is degraded more quickly than the other in the environmental matrices studied. In the resubmission application soil degradation rate estimates were updated following the recommendations of the FOCUS kinetics guidance, with normalisations to FOCUS reference conditions (20ºC / -10kPa soil moisture) with both laboratory and field investigations being normalised for temperature using a Q10 of 2.58. Only Laboratory investigations were normalised for moisture content. This was done using the Walker equation coefficient of 0.7. A new OECD 106 guideline soil adsorption study for myclobutanil

butyric acid, that determined Freundlich adsorption parameters was also provided. Environmental exposure estimates for the representative use assessed in the resubmission (grapes) were updated consequent to these new assessments. In the resubmission, the environmental exposure assessment for the original applied for intended use on apples was not updated as this use was no longer supported by the applicant in their dossier supporting their resubmission application for annex 1 listing. Therefore data gaps for an anaerobic soil incubation or environmental exposure estimates (predicted environmental exposure concentrations (PEC)) that relate to a use on apples are not included in Appendix A or considered in the sections of this conclusion regarding: the list of studies to be generated, assessments not finalised or critical areas of concern.

6.6.1 4.1. Fate and behaviour in soil

4.1.1. Route of degradation in soil

Soil experiments (three different soils) were carried out under aerobic conditions in the laboratory (20°C, 40% maximum water holding capacity (MWHC)) in the dark with myclobutanil applied as test substance. The formation of residues not extracted by acidified acetonitrile:water were a sink for the applied chlorophenyl (one soil tested) and triazole ring-^{14}C-radiolabels (all three soils tested) which accounted for 4 to 16% of the applied radiolabel (AR) after 120 days. Mineralisation to carbon dioxide of the triazole ring-^{14}C-radiolabel accounted for only 0.2 to 1.6% AR, whilst for the chlorophenyl ring-^{14}C-radiolabel this value was 1.7% AR (both after 120 days). The most significant but minor (<10% AR) extractable breakdown product present was myclobutanil butyric acid (maximum 6% AR at 76 days). At 120 days (study end) myclobutanil still accounted for 80 to 92% of the applied radioactivity.

Data on anaerobic degradation in soil were not available. However these data are not necessary to complete an assessment for the representative use on grapes as the experts agreed that grapes are unlikely to be cultivated under geoclimatic conditions where soils will become saturated and consequently anaerobic. However the experts considered this could not be excluded for the representative use on apples. The experts therefore identified a data gap for an anaerobic soil metabolism study to support the applied for use on apples.

Though a laboratory soil photolysis study was available there was agreement by the experts that the study was not reliable with respect to the amount of metabolites formed (identified metabolite accounted for a maximum of 4% AR) and the photolysis rate of degradation due to the low light energy and narrow wavelength range provided by the lamp in the experiment. They however felt that there was no reason to challenge the identification of the metabolite (RH-9089) characterised as being formed under the experimental conditions of the study. They also considered the fact that the myclobutanil molecule does not absorb light energy above 290nm to indicate direct soil photolysis will not occur, so the limited degradation observed in the available study would result from indirect photolytic processes which may not be a very reproducible phenomenon. In line with a PPR panel opinion the experts agreed that due to the low light absorbance of the myclobutanil molecule, soil photolysis would not be expected to be a significant process contributing to the degradation of myclobutanil and consequently a new soil photolysis study was considered unnecessary.

4.1.2. Persistence of the active substance and their metabolites, degradation or reaction products

The rate of degradation of myclobutanil was estimated from the results of the studies described in 4.1.1 above. DT_{50} were: 191 to 1216 days (single first-order non-linear regression, 20°C 40% MWHC, three different soils). Laboratory rate of degradation experiments dosed with myclobutanil were available on a further three different soils. DT_{50} were: 191 to 354 days (single first-order non-linear

regression, 22°C, percent MWHC not reported). After normalisation to FOCUS reference conditions[13] (20°C and -10kPa soil moisture content when the experimental soil moisture was reported), this range of single first-order DT_{50} becomes 149 to 1092 days (geometric mean that is appropriate for use in FOCUS modelling 305 days). Clearly as the duration of these experiments was 120 to 161 days there is greater than usual uncertainty in these DT_{50} values since they are all extrapolated beyond the durations of these laboratory studies.

The minor (maximum 6% AR) soil degradation product of myclobutanil, myclobutanil butyric acid was applied as test substance to four soils and incubated in the laboratory (aerobic dark 25°C and 1/3 bar soil water holding capacity WHC for two soils and slightly below 1/3 bar WHC for the other two soils, note the fact that two of the soils had a lower moisture content was not reported in the DAR). Single first-order DT_{50} values from these studies were calculated to be 5 to 42 days (5, 7, 22 and 42 days). After normalisation to FOCUS reference conditions (20°C and -10kPa soil moisture content using the same methodology as described above for the active substance) these values were 7.4 to 40.4 days (7.4, 9, 26 and 40.4 days; geometric mean that is appropriate for use in FOCUS modelling 16.2 days). The experts at the meeting noted that in the experiment (LUFA 3A loam soil) dosed with myclobutanil (myclobutanil first-order DT_{50} 191 days) which had the maximum observed formation of myclobutanil butyric acid (6% AR), that the kinetic formation fraction of myclobutanil butyric acid from myclobutanil was ca. 0.6 or 60%.

From discussions at the PRAPeR 12 meeting in January 2007 it was identified that the potential (but very minor as not detected in the available appropriately radiolabelled studies) soil metabolite 1,2,4-triazole degrades in laboratory soil experiments with single first-order DT_{50} of 6 to 12 days (20°C 40% MWHC, three different soils, normalised to FOCUS reference conditions (-10kPa soil moisture content single first-order DT_{50} 5 to 10 days)). Because of this relatively rapid transformation rate compared to the breakdown rate of myclobutanil, soil residues of this metabolite would be expected to present at only very low levels.

Field soil dissipation studies (bare soil) were provided from four sites in Germany where applications were made at the end of May and the beginning of June. Using the residue levels of parent myclobutanil determined over the whole core sampled (0 to 20cm soil layer), DT_{50} were estimated to be 9 to 58 days with DT_{90} being greater than a year. Only at one study site had the residue declined to <10% of the initial measured concentration at the last sampling time (368 to 387 days after application). The pattern of degradation was clearly biphasic but calculated DT_{90} values were not presented in the DAR (only noted as being >1 year). In the addenda to the DAR the results of normalising the field DT_{50} from these field trials to reference conditions of 20°C (but not soil moisture content) using the modified day length approach assuming first-order kinetics[14] and non-linear regression was reported. However the experts at PRAPeR 17 were not able to assess the goodness of fit resulting from this exercise, as plots of the decline curves were not provided in the addendum available to the experts attending the meeting. It was not clear to the experts if the normalisation procedure that resulted in the biphasic degradation pattern observed in the not normalised kinetic fitting subsequently became adequately described by first-order kinetics, as was assumed by the fitting procedure used. Only r^2 values were reported by the rapporteur Member State in the addendum to indicate how representative the estimated normalised first-order DT_{50} were and this not particularly robust measure of reliability of the estimated DT_{50} values, indicates that the fits may not be acceptable (low r^2 values 0.322, 0.696, 0.736 and 0.776). The experts agreed that it was not possible to use these normalised first-order field DT_{50} values as the basis of the environmental exposure estimate in the absence of a visual inspection of the fitted curves, to refute the indication given by the low r^2 values that these estimated DT_{50} were too unreliable. EFSA was subsequently able to confirm that the pattern

[13] Using section 2.4.2 of the generic guidance for FOCUS groundwater scenarios, version 1.1 dated April 2002 and a Q10 of 2.58 in line with Opinion on a request from EFSA related to the default Q10 value used to describe the temperature effect on transformation rates of pesticides in soil Scientific Opinion of the Panel on Plant Protection Products and their residues: The EFSA Journal (2007) 622, 1-32.
[14] as described in FOCUS (2006). This exercise used a Q10 of 2.2.

of decline following normalisation (as graphically presented in the original study report[15]) was not well described by first-order kinetics and still showed a biphasic pattern of decline, as was suspected by the experts at the meeting. In the resubmission application, a new normalisation of the field studies using the modified day length approach to the FOCUS reference temperature of 20ºC using a Q10 of 2.58 that fitted double first order in parallel (DFOP) kinetics was presented. It was concluded as appropriate to use the geomean of the second phase rate constants from the DFOP fits for deriving the DT_{50} to be used as input in the FOCUS leaching models. This is the approach the FOCUS work group on degradation kinetics, document recommends. This DT_{50} value for myclobutanil is 228 days.

In field accumulation studies carried out at one site in Germany (bare soil application) and one site in California (air assisted broadcast spray applications to grapes) concentrations increased following the first 2 and 3 years of applications respectively. Further applications in subsequent years did not result in any further accumulation.

The arithmetic mean of the single first-order soil DT_{50} from the myclobutanil laboratory incubations on the Lufa 2.1 soil (replicated experiments with different radiolabel positions) after normalisation to FOCUS soil moisture reference conditions (-10kPa) of 711.5 days (highly extrapolated value, in the soil that resulted in the longest DT values) was selected by the RMS and accepted for use in PEC_{soil} calculations (as the pattern of biphasic decline observed in the field studies without normalisation to a reference soil temperature of 20ºC was not adequately characterised in any of the available assessments). As required for this persistent substance, these PEC soil calculations included an assessment of accumulation from use in successive years (see Appendix A).

4.1.3. Mobility in soil of the active substance and their metabolites, degradation or reaction products

The adsorption / desorption of myclobutanil was investigated in five soils in satisfactory batch adsorption experiments, that determined Freundlich isotherms. Calculated adsorption K_{Foc} values varied from 226 to 920 mL/g, (mean 517 mL/g) (1/n 0.85 to 0.91, mean 0.88). There was no evidence of a correlation of adsorption with pH.

The adsorption / desorption of myclobutanil butyric acid was investigated in five soils in satisfactory batch adsorptions experiments that determined Freundlich isotherms. These data were provided in the resubmission application and supersede the previously available estimates that had only investigated a single soil water concentration, that had previously only enabled K_{doc} to be estimated. Calculated adsorption K_{Foc} values were 5.3 to 26.7 mL/g (mean 13.2 mL/g) (1/n 0.82 to 1.07, mean 0.95). There was no evidence of a correlation of adsorption with pH.

From discussions at the PRAPeR 12 meeting in January 2007 it was identified that the potential (but very minor, not detected in the available appropriately radiolabelled studies) soil metabolite 1,2,4-triazole has K_{Foc} values estimated from satisfactory batch adsorption experiments in four soils of 43 to 120 mL/g, (mean 89 mL/g) (1/n 0.83 to 1.02, mean 0.92). There was no evidence of a correlation of adsorption with pH.

6.6.2 4.2. Fate and behaviour in water

4.2.1. Surface water and sediment

Myclobutanil was essentially stable under sterile hydrolysis conditions at 50°C at pH 4, 7 and 9. Myclobutanil will not undergo direct aqueous photolysis as there is no significant absorption by the molecule at wavelengths ≥ 290 nm.

[15] Page 40, Reeves G., (2006) Modelling the leaching of myclobutanil and a potentially relevant metabolite (ß-4-chlorophenyl-ß-cyano-γ-(1*H*1,2,4-triazole)butyric acid) to groundwater in the EU using PEARL and the FOCUS scenarios. Report No: GHE-P-11416.

A ready biodegradability test (OECD 301D) indicated that myclobutanil is 'not readily biodegradable' using the criteria defined by the test.

In water-sediment studies (two systems studied at 20°C in the laboratory) myclobutanil dissipated by partitioning to sediment (observed water decline single first-order DT_{50} 4 days where sediment organic carbon content (OC) was 3.18% and 20 days where sediment OC content was 0.62%). Subsequent degradation in sediment was slow (whole system single first-order DT_{50} was 415 days for the lower OC system and 838 days in the higher OC system, both estimates are uncertain as they are extrapolated significantly beyond the study duration of 105 days, arithmetic mean value 626 days). No single metabolite (five resolved by chromatography) accounted for >4.7% AR in either the water or sediment compartment of the experiment. None were identified. The terminal metabolite, CO_2, accounted for only 0.3% AR of the triazole ring radiolabel by 105 days. Residues not extracted from sediment by acidified acetonitrile and Soxhlet extraction were a sink representing 4.3 to 9.8% AR at study end (105 days), though of course the major sink for the applied radioactivity was parent myclobutanil extracted from the sediment. The experts agreed that for sediment a myclobutanil single first-order DT_{50} of 626 days (arithmetic mean whole system values) and for water a default value of 999 days were acceptable for use as FOCUSsw scenario calculation input. They also agreed the calculation for accumulated concentrations in sediment as set out in the addendum that also used a sediment DT_{50} of 626 days.

PEC surface water to static water bodies from just spray drift were presented in the DAR. These were not appropriate for use in the EU level assessment that requires FOCUS surface water approaches to be used.

For myclobutanil, FOCUS surface water modelling was evaluated up to step 3 for the use on grape grapes (late growth stages highest potential for spray drift) and steps 3 (pond scenarios) and 4 (stream and ditch scenarios) for the use on apples (early growth stages highest potential for spray drift). The peer review at PRAPeR 17 noted that the soil DT_{50} used in calculations (282 days) was shorter than the available reliable lab data indicate is appropriate (306 days) but concluded that this would not effect the PEC values as the pesticide application timer (PAT) algorithm ensures drainage and runoff events occur shortly after application and the exposure is driven by spray drift and not myclobutanil moving from soil. The peer review of the original application/dossier therefore agreed these PEC surface water as presented in the updated DAR for multiple applications and in the addendum for single applications (where this was the highest calculated value) were appropriate for use in risk assessment (in line with FOCUS guidance). At step 4 (apple use) the only mitigation considered was no spray drift buffer zones of 12 and 14 m that were implemented following the methods prescribed by FOCUSsw guidance. For sediment PEC the accumulated concentrations from the defined number of applications per year and use in successive years were calculated in the addendum using FOCUS step 3 default buffer distances for both grapes and apples for the FOCUS scenarios that gave the highest PEC_{sed} (apples D4 pond and grapes D6 ditch, see updated DAR). The PRAPeR 17 peer review agreed these PEC_{sed} as appropriate for use in risk assessment and would encompass the expected sediment concentrations at all the other FOCUS scenarios. These simulations utilised a Q10 of 2.2. In the resubmission application only the PEC calculations for surface water and sediment from the use on grapes were updated. The approach followed for myclobutanil was as described above except the laboratory geomean soil DT_{50} of 305 days, water DT_{50} of 415 days and sediment DT_{50} of 1000 days was employed for the PECsw. These simulations utilised the Q10 of 2.58. Accumulated myclobutanil PEC sediment for D6 ditch were calculated as discussed above using a sediment DT_{50} of 626 days (arithmetic mean whole sediment water system value). Step 1 and 2 calculations were also presented for myclobutanil butyric acid, though as this PEC is lower than the PEC groundwater, so this latter PEC was used to finalise the aquatic risk assessment for myclobutanil butyric acid. These PEC are presented in Appendix A.

4.2.2. Potential for ground water contamination of the active substance their metabolites, degradation or reaction products

The substance input parameters for groundwater modelling appropriate for use in FOCUS scenario groundwater modelling identified by the PRAPeR 17 peer review meeting from the acceptable data available then, were a myclobutanil single first-order DT_{50} 306 days (laboratory experiment derived value), K_{Foc} 517 mL/g, 1/n=0.88; myclobutanil butyric acid single first-order DT_{50} 15.1 days, kinetic formation fraction from myclobutanil of 0.6 (60%) and K_{doc} of 36 mL/g, 1/n=1. This meeting of experts maintained the data requirement for further FOCUS scenario groundwater exposure modelling to be provided as none of the available simulations used substance parameters considered comparable to these. In any new modelling it might be possible to utilise appropriate myclobutanil DT_{50} derived from field dissipation studies normalised to reference conditions, if the approach used was reported in a transparent way and strictly adhered to all pertinent FOCUS kinetics guidance recommendations (particularly those relating to handling the results from field experiments that indicate a biphasic pattern of disappearance). The experts' concerns regarding the then available exercise to normalise field dissipation study DT_{50} values and reasons why the results of this exercise could not be used for the assessment at that time are already described in detail in section 4.1.2. Following the resubmission application the substance input parameters for groundwater modelling appropriate for use in FOCUS scenario groundwater modelling were then identified as a myclobutanil single first-order DT_{50} 228 days (FOCUS reference temperature[16] second slow phase geomean DT_{50} from field studies (DFOP fitting), there was no normalisation for soil moisture), K_{Foc} 517 mL/g, 1/n=0.88; myclobutanil butyric acid single first-order DT_{50} 16.2 days, kinetic formation fraction from myclobutanil of 0.6 (60%) and K_{Foc} of 13.2 mL/g, 1/n=0.95.

On the basis of the available groundwater simulations as described in the DAR and addendum available before the resubmission application that utilised more favourable substance property parameters than were appropriate[17] (most significantly myclobutanil DT_{50} that is too short and myclobutanil butyric acid kinetic formation fraction one tenth the appropriate value) the parent myclobutanil was calculated to be present in leachate leaving the top 1 m soil layer at 80th percentile annual average concentrations in the range <0.001 to 1.16 µg/L for apples with 7 out of 9 scenarios being >0.1 µg/L. The equivalent now superseded values for grapes were <0.001 to 0.517 µ/L with 6 out of 7 scenarios being >0.1 µg/L. For myclobutanil butyric acid this range was <0.001 to 0.03 µg/L for apples. The equivalent now superseded values for grapes were <0.001 to 0.021 µ/L. Although these values for myclobutanil butyric acid are all < 0.1 µg/L, if an appropriate kinetic formation fraction had been used in simulations, EFSA expected the 0.1 µg/L trigger would be exceeded in the majority of FOCUS scenarios and it could not be excluded that a concentration of >0.75 µg/L would occur in some scenarios. This expectation for myclobutanil butyric acid was confirmed in the resubmission application, where appropriate groundwater simulations were carried out, for the representative use assessed on grape grapes. These PEC for myclobutanil and the butyric acid metabolite (that utilised both the FOCUS PEARL 3.3.3 and FOCUS PELMO 3.3.2 models and a Q10 of 2.58) are presented in Appendix A. These simulations indicate that groundwater exposure by myclobutanil above the parametric drinking water limit of 0.1 µg/L, will not occur in geoclimatic situations represented by 6 out of the 7 pertinent FOCUS groundwater scenarios. In geoclimatic situations represented by just the Piacenza grape scenario, groundwater exposure might occur with concentrations (annual average recharge leaving the top 1m soil layer) estimated to be 0.21 µg/L. For the metabolite myclobutanil butyric acid, groundwater exposure above the parametric drinking water limit is expected in geoclimatic situations represented all 7 pertinent FOCUS groundwater grape vine scenarios. In geoclimatic situations represented the FOCUS Hamburg grape vine groundwater scenario concentrations > 0.75 µg/L (a key assessment trigger from the groundwater metabolite relevance guidance document) might be expected. The estimated concentration at this scenario was

[16] Normalised assuming a Q10 of 2.58.

[17] The more favourable values were a myclobutanil single first-order DT_{50} 282 or 250 days (laboratory), adsorption values as agreed by the peer review; myclobutanil butyric acid single first-order DT_{50} 14.5 days, kinetic formation fraction from myclobutanil of 0.06 (6%) and K_{doc} as agreed by the PRAPeR 17 peer review meeting, 1/n=0.9.

0.816µg/L. A groundwater metabolite non relevance assessment was therefore triggered for myclobutanil butyric acid.

As the potentially very minor soil metabolite 1,2,4-triazole was not detected in any of the soil route of degradation studies and it degrades relatively quickly compared to myclobutanil (see 4.1.2), it can be concluded that the potential for 1,2,4-triazole to reach groundwater from the application of myclobutanil is negligible.

6.6.3 4.3 Fate and behaviour in air

The vapour pressure of myclobutanil (1.98×10^{-4} Pa at 20°C) means that myclobutanil would be classified under the national scheme of The Netherlands as slightly volatile, indicating limited losses due to volatilisation might be expected. Based on the results of a laboratory wind tunnel experiment where a myclobutanil formulation were applied to a soil and dwarf runner beans, it was estimated that up to 2.6% of the myclobutanil applied was lost (assumed to the air compartment but only loss from the treated matrix was measured) from bean plants in 24 hours, losses from soil were negligible. Calculations using the method of Atkinson for indirect photooxidation in the atmosphere through reaction with hydroxyl radicals resulted in an atmospheric half life estimated at 7.6 hours (assuming an atmospheric hydroxyl radical concentration of 1.5×10^{6} radicals cm^{-3}) indicating the small proportion of applied myclobutanil that will volatilise would be unlikely to be subject to long range atmospheric transport.

5. Ecotoxicology

Myclobutanil was discussed at the PRAPeR experts' meeting for ecotoxicology in March 2007 (PRAPeR 18). Information on the composition of the batches used in the ecotox studies was missing and a data requirement was identified. Information on three batches out of ten was made available by the applicant before the expert meeting. The experts agreed to leave the data requirement open since information on the remaining seven batches was missing. Furthermore a data gap was identified for the submission of information on the ecotoxicological relevance of impurities 3, 8 and 14. This information was provided in the resubmission dossier and evaluated by the RMS. It is highly unlikely that the increased levels of the impurities compared to the levels found in the batches used in the ecotox tests would lead to a significant increase in the risk to non-target organisms. The maximum limits specified are considered to be sufficiently covered by the ecotox data package.

In the risk assessment it was not specifically considered that myclobutanil is a racemic mixture. It should be noted that this adds some unquantified uncertainty to the outcome of the risk assessment. The impact of different isomer ratios on the environmental risk assessment of myclobutanil is to be addressed. No new studies or information was provided in the resubmission dossier. Therefore the data gap is maintained.

Direct toxic effects on the liver led to different secondary adverse effects including effects on endocrine regulation. The effects (endocrine effects observed in mammals were secondary effects as a consequence of direct toxic effects in the liver.

The use in apples was withdrawn for the resubmission by the applicant. The assessment of the apple use was retained in the conclusion for information only.

6.6.4 5.1. Risk to terrestrial vertebrates

The representative uses of myclobutanil evaluated in the first peer-review are as fungicide on grapes with four applications of 0.048 kg/ha, and on apples with four applications of 0.090 kg/ha per season. The risk to insectivorous birds and small herbivorous mammals was assessed for the orchard/vine/hop scenario in accordance with SANCO/4145/2000. For birds all TER values were well above the relevant Annex VI trigger, thus indicating a low risk.

The first tier risk assessment for small herbivorous mammals from use on grapes resulted in acute TER of 176 and long-term TER of 5.18. Since these values meet the Annex VI triggers of 10 and 5, respectively, the risk is considered as low. For the use on apples the acute TER was 94 and the long-term TER 2.8, hence indicating a first-tier high long-term risk.

The long-term risk assessment for mammals was refined in the DAR by applying an interception factor of 70%, which is applicable for apples at the stage of foliage development and on vine at flowering. However, the applicant has indicated that two applications are foreseen also at the stage of flowering in apples. At this stage interception is 65% according to the generic guidance for FOCUS ground water scenarios SANCO/321/2000 rev.2. The experts suggested that the long-term risk should be recalculated for four applications and interception factors of 65% and 70%. The rapporteur Member State recalculated the long-term TER for herbivorous mammals as 5.18 according to the suggestions made in the expert meeting. The resulting TER of 5.18 exceeds the trigger of 5. The acute and long-term risk to small herbivorous mammals is low for all representative uses evaluated.

Triazolyl alanine and triazolyl acetic acid were detected in plants as the two main plant metabolites of myclobutanil. The acute oral toxicity of these metabolites was less than or comparable to that of myclobutanil. The NOAEL for developmental effects of triazolyl alanine was higher than for myclobutanil. Studies on developmental and reproductive toxicity are not available for triazolyl acetic acid. However the plant metabolites were also formed in the rat metabolism studies and hence the risk from the metabolites to herbivorous mammals is considered to be covered by the risk assessment for myclobutanil.

The determination of log P_{ow} for myclobutanil was inconclusive but it cannot be excluded that it would be greater than 3. A study on bioaccumulation in earthworms is available, showing a low BCF value of 0.46 to 0.47 and the risk from secondary poisoning of earthworm-eating birds and mammals is therefore considered to be low. A bioconcentration study with fish was not available in the first peer-review and the potential for secondary poisoning of fish-eating birds and mammals has not been assessed in the DAR. A data gap for submission of a bioconcentration study with fish was identified in the expert meeting in the first peer-review.

TER calculations were provided for the use in vineyards in the resubmission dossier. The TER calculation for fish-eating birds and mammals were based on a (whole body) BCF of 8.3 derived in a fish bioconcentration study. The TERs were well above the trigger indicating a low risk to fish-eating birds and mammals.

Since the application of myclobutanil is not intended for leafy crops, the rapporteur Member State did not consider a risk assessment for intake of contaminated drinking water as necessary. However it was agreed in previous expert meetings that an acute TER according to SANCO 4145/2000 should be conducted. The acute TER was calculated for the higher application rates in apples as 105 for birds and 618 for mammals by the rapporteur Member State in the updated version of the DAR from June 2007 (not peer reviewed). Since the application rate in vineyards is lower the risk is covered by the assessment for the apple use.

Concerns with regard to endocrine mediated adverse effects in birds and mammals were raised in the first-peer review. The applicant was requested to submit further information to address the risk from endocrine effects. The effects observed in mammals were direct toxicity on liver which led to secondary effects including effects on steroid homeostasis. No significant effects on reproduction were observed in the 2-generation rat study at a dose of 16 mg/kg bw/d. A LOEL of 2.5 mg/kg bw/d was observed in a rat carcinogenic study. Testicular atrophy was observed at late life stage of rats (effects became apparent after 12 months of exposure) and therefore the effect was not considered to be of relevance in the context of wildlife risk assessment. The experts considered the endpoint of 16 mg/kg bw/d as appropriate for the long-term risk assessment for mammals.

The NOEL from the bird reproduction study was 24.2 mg a.s./kg bw/d. It was noted that there is a good chance to detect endocrine mediated effects on reproduction in the study if the endocrine effect

become manifest already in the first generation. However it is unclear whether birds would be exposed during all relevant stages of their development and if other relevant endocrine-sensitive endpoints such as behaviour would be detected (e.g. parental care, nesting behaviour, territoriality and mounting behaviour). There was no indication from the mammalian studies that effects would appear only in the second generation but not in the first generation. No information on endocrine disruption of myclobutanil in birds was found by the RMS in public literature. The experts agreed that the NOEL of 24.2 mg a.s./kg bw/d may be sufficiently conservative and no additional safety factor needs to be applied to cover potential endocrine effects.

In summary, it can be concluded that the risk to wild birds and mammals from exposure to myclobutanil under conditions of the intended representative uses is low.

6.6.5 5.2. Risk to aquatic organisms

Myclobutanil is very toxic to aquatic invertebrates, with the lowest EC_{50} of 0.24 mg a.s./L obtained for *Mysidopsis bahia.* Available studies do not indicate that the formulation 'Systhane 20 EW' is significantly more toxic than what could be expected based on the content of myclobutanil.

The first-tier acute TER values were calculated as the ratio of the toxicity to PEC_{max} in surface water for the different FOCUS scenarios that are applicable to the proposed uses. For the assessment of chronic risk 21 d TWA PEC_{sw} was used in the DAR. A NOEC of 0.2 mg/L for rainbow trout (*Oncorhyncus mykiss*) was derived in a 21-day juvenile growth test with no effects observed in the highest concentration tested. A $NOEC_{growth}$ of 0.98 mg/L for fathead minnow (*Pimephales promales*) from an early life stage study is also available. The choice of end point for the risk assessment was discussed in the experts' meeting and the majority of the experts proposed to use the value of 0.2 mg a.s./L since rainbow trout was the most sensitive species for acute toxicity. The member state experts agreed to use the global maximum PEC_{sw} for the TER calculation since the time window on which the time weighted average PEC_{sw} should be calculated was not determined by observations on the time to onset of effects.

Myclobutanil belongs to the group of de-methylation inhibitor (DMI) fungicides which are suspected to cause endocrine effects in fish. In the meeting of experts it was agreed that an additional safety factor of 5 (as for other triazoles) should be applied to the early life stage (ELS) test or to the juvenile growth test with fish (approach developed by Germany for national authorisation). The experts concluded that the endpoint of 0.04 mg a.s./L (0.2 mg a.s./L divided by the safety factor of 5) should be used in the risk assessment together with initial PECsw. This was considered as a conservative approach since the NOEC was set at the highest tested concentration. The TERs were above the trigger of 10 for all FOCUS scenarios. The expert from Germany noted that a fish sexual development test (FSDT) was required at national level as a post registration requirement.

For the use on vine the FOCUS R4 stream scenario (PEC_{sw} = 1.956 µg a.s./L) was the worst case scenario. The TER values for all groups of aquatic organisms were above the Annex VI trigger and thus a low acute and chronic risk can be concluded for the use on vine.

Myclobutanil was detected in sediment at concentrations of 66 to 85% of applied at the end of the water/sediment study. A water spiked study with *Chironomus riparius* is available to assess the risk to sediment dwelling organisms. The NOEC of 4.98 mg a.s./L derived from the study was recalculated to 6.07 mg a.s./kg sediment in the DAR and compared to 21 d TWA PEC values for the different FOCUS scenarios. The expert meeting agreed that the NOEC of 6.07 mg a.s./kg sediment should be compared with the worst case maximum PEC_{sed} from FOCUS modelling. The TER values were well above the Annex VI trigger of 10 based on worst case PEC_{sed} values of 8.77 µg a.s./kg (FOCUS step 3+accumulation calculation, D6 ditch) for the use on grapes.

No major metabolites were detected in the water/sediment study, and no major metabolites that potentially could contaminate surface water via drainage or run off were detected in the soil degradation studies. However in the situation where groundwater may become surface water, a risk

assessment to aquatic organisms is required for myclobutanil butyric acid. The risk to aquatic organisms from this route of exposure is considered to be low since myclobutanil butyric acid is more than 3 orders of magnitude less toxic to fish and aquatic invertebrates and about 1 order of magnitude less toxic to algae compared to myclobutanil. The TER value for the most sensitive species tested (algae, E_bC_{50} = 56.2 mg/L) would be 68,873 when compared to the undiluted concentration from the worst-case groundwater scenario Hamburg (PEC_{gw} = 0.816 µg/L) .

The assessment of log P_{ow} for myclobutanil was inconclusive and the experts' meeting considered it necessary to require a bioconcentration study with fish since four applications are foreseen and chronic and repeated exposure cannot be excluded. A fish bioconcentration study was included in the resubmission dossier. The whole fish BCF was estimated as 8.3 suggesting a low risk of bioconcentration and bioaccumulation.

Overall it is concluded that the risk to aquatic organisms is low for the use on grapes.

6.6.6 5.3. Risk to bees

The oral and contact toxicity of the formulation 'Systhane 20 EW' to bees is low. The HQ values are in the range 1.2 to 2.6 for single applications. The risk to honeybees was considered as low from the intended uses.

6.6.7 5.4. Risk to other arthropod species

The dose rates applied in the first-tier studies with *Typhlodromus pyri, Aphidius rhopalosiphi, Coccinella septempunctata* and *Pardosa* did not cover the maximum application rates on apples and vine 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.

A semi-field study in which hop plants were treated with four applications of 'Systhane 20 EW' (4 × 54 g a.s./ha and 4 × 300 g a.s./ha) did not show any significant effects on behaviour or reproductive capacity of *A. rhopalosiphi*. Effects of 'Systhane 20 EW' on *T. pyri* were tested in field trials in an apple orchard in southern Germany with 9 × 180 g a.s./ha. No effects on predatory mite eggs and adults were observed. The study was discussed in the experts' meeting and considered to be valid. Additionally, an extended study with *Crysoperla carnea* showed no effects of greater than 50% on mortality or reproduction at rates of 766 g a.s./ha and 1380 g a.s./ha. Therefore, the risk to non-target arthropods was considered to be sufficiently addressed and no further studies are required.

6.6.8 5.5. Risk to earthworms

The acute risk to earthworms was assessed by comparing the LC_{50} for technical myclobutanil with the maximum peak PEC_{soil} of 0.428 mg a.s./kg soil (grapes) after last application on top of the average plateau concentration calculated for repeated application during several years. Acute TER values were 292 and 115 for the use in grapes. The long-term risk was assessed by comparing the NOEC from a reproduction study with the formulation 'Systhane 20 EW' with the average plateau PEC_{soil}. It is the EFSA view that for the first-tier assessment, also the risk for long-term/reproduction effects should be assessed by comparing the NOEC with the peak PEC_{soil} following the last application on top of the plateau concentration. This would result in long-term TER values of 12 for the use in grapes. Since all TER values are above the relevant Annex VI trigger the risk to earthworms can be considered as low.

Additionally an acute study with the minor soil metabolite myclobutanil butyric acid showing lower toxicity to earthworms than myclobutanil is available.

From a bioconcentration/depuration study, using myclobutanil ^{14}C-labbeled at the chlorophenyl ring, the BCF in earthworms was determined to be 0.46. This indicates that myclobutanil does not readily bioconcentrate in earthworm tissue.

6.6.9 5.6. Risk to other soil non-target macro-organisms

The DT_{90} value in soil for myclobutanil in laboratory and field studies is greater than 1 year and hence studies on organisms contributing to organic matter breakdown are required. A reproduction study with *Folsomia candida* using 'Systhane 20 EW' is available. Based on the corrected NOEC of 10.25 mg a.s./kg soil a TER value of 23.9 was derived using the peak PEC_{soil} of 0.428 mg a.s./kg soil (grapes). The risk to collembolan species can therefore be considered as low.

A litter bag study was triggered based on the persistence of myclobutanil in soil. The study by Galicia (2002) was evaluated as not acceptable by the rapporteur Member State. The experts agreed with this assessment since no positive control was used and the test substance concentrations were not measured. The study of Mallet (2004) was considered acceptable. No effects on organic matter breakdown was observed in the test at the measured concentrations of 0.1247 to 0.1460 mg a.s./kg soil. This concentration covers the PEC_{soil} after one year of use on grapes. The tested concentration is clearly below the peak PEC_{soil} of 0.428 mg a.s./kg soil. However, taking into account that no effects were observed in the litter bag study and that the risk to earthworms and collembola was assessed as low it is assumed that the risk to soil-dwelling non-target macro-organisms is low and no new litter bag study is considered necessary.

6.6.10 5.7. Risk to soil non-target micro-organisms

Effects on soil nitrogen transformation and soil respiration were studied using the formulation 'Systhane 24E' which is considered as comparable to the lead formulation. No deviations >25% compared to the control were observed at soil concentrations of 2.93 mg formulation/kg soil. This concentration corresponds to 0.7 mg a.s./ha and covers the peak PEC_{soil}.

6.6.11 5.8. Risk to other non-target-organisms (flora and fauna)

Results from vegetative vigour and seedling emergence tests with four monocotyledon and six dicotelydon species using 'Systhane 20 EW' indicate that the risk to non-target plants is low for the evaluated uses on vine and apple. The highest effect in the vegetative vigour test was 60% inhibition of shoot weight at 900 g a.s./ha for *Brassica oleracea.* In the seedling emergence test 33% inhibition of shoot weight was observed for *Lolium perenne* at a dose rate of 300 g a.s./ha.

6.6.12 5.9. Risk to biological methods of sewage treatment

The EC50 was determined to 71 mg a.s./L in an activated sludge respiration inhibition test. Since this is significantly higher than the PECsw no adverse effects on biological methods of sewage treatment are expected should myclobutanil reach sewage treatment plants.

6. Residue definitions

6.6.13 6.1. Soil

Definitions for risk assessment: myclobutanil

Definitions for monitoring: myclobutanil isomers

6.6.14 6.2. Water

6.2.1 Ground water

Definitions for exposure assessment: myclobutanil and myclobutanil butyric acid

Definitions for monitoring: myclobutanil isomers

6.2.2 Surface water

Definitions for risk assessment: water: myclobutanil and myclobutanil butyric acid sediment: myclobutanil

Definitions for monitoring: myclobutanil isomers

6.3 Air

Definitions for risk assessment: myclobutanil

Definitions for monitoring: myclobutanil isomers

6.4 Food of plant origin

Definitions for risk assessment: myclobutanil, RH-9090[18] free and conjugated expressed as myclobutanil (limited to category of fruit crops only)

Definitions for monitoring: myclobutanil isomers (limited to category of fruit crops only)

6.5 Food of animal origin

Definitions for risk assessment: no conclusion possible with the available data; not required for the representative use in grapes in the resubmission procedure.

Definitions for monitoring: no conclusion possible with the available data; not required for the representative use in grapes in the resubmission procedure.

[18] RH-9090: (2*RS*,5*RS*) 2-(4-chlorophenyl)-5-hydroxy-2-(1*H*-1,2,4-triazol-1-ylmethyl)hexanenitrile

6. Overview of the risk assessment of compounds listed in residue definitions for the environmental compartments

6.6.1 Soil

Compound (name and/or code)	Persistence	Ecotoxicology
myclobutanil	High to very high persistence Single first-order DT_{50} 191 to ~~574~~ 1216 days (20 to 22°C, 40%MWHC or not reported soil moisture) Biphasic, DT_{50} 9 to 58 days, DT_{90} >1 year (German field studies)	The risk to soil dwelling organisms was assessed as low.

6.6.2 Ground water

Compound (name and/or code)	Mobility in soil	> 0.1 µg / L 1m depth for the representative uses (at least one FOCUS scenario or relevant lysimeter)	Pesticidal activity	Toxicological relevance	Ecotoxicological relevance
myclobutanil	Medium to low mobility K_{Foc} 226 to 920 mL/g	At 6 of the 7 scenarios for grapes, concentrations are below 0.1 µg/L. At the 7th (Piacenza) concentrations were estimated to be up to 0.21µg/L	Yes	Yes	Very toxic to aquatic organisms. The risk to aquatic organisms in surface water was assessed as low.
myclobutanil butyric acid	Very high mobility K_{Foc} 5.3 to 26.7 mL/g	Concentrations will exceed 0.1 µg/L at all 7 scenarios for grapes, with concentrations exceeding 0.75 µg/L but at just the Hamburg scenario, where concentrations were estimated to be up to 0.816µg/L.	None at the pertinent appropriate dose levels investigated	No; *in vitro* and *in vivo* genotoxicity studies, overall showing no genotoxic potential; maternal and developmental toxicity NOAELs>450mg/kg bw/day	Approximately one order of magnitude less toxic to aquatic organisms compared to myclobutanil. The risk to aquatic organisms in surface water was considered as low.

6.6.3 Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Myclobutanil (water and sediment)	Very toxic to aquatic organisms. All TERs are above the Annex VI trigger for the uses in grapes. No spray buffer zones of up to 14 metres are required for the use in apple orchards.
myclobutanil butyric acid, in the situations where groundwater becomes surface water.	More than 3 orders of magnitude less toxic to fish and daphnids and about one order of magnitude less toxic to algae compared to myclobutanil. The risk to aquatic organisms in surface water was assessed as low.

6.6.4 Air

Compound (name and/or code)	Toxicology
myclobutanil	Not acutely toxic via inhalation.

LIST OF STUDIES TO BE GENERATED, STILL ONGOING OR AVAILABLE BUT NOT PEER REVIEWED

Information on the comparability of the toxicological studies performed with technical material of different purity is required, as well as toxicological information on impurities (relevant for all representative uses evaluated; no submission date proposed by the applicant; data gap identified by the meeting of experts; refer to section 2 Mammalian toxicology).

Impact of different isomer ratios on the exposure assessment of myclobutanil for operator, worker and bystander to be addressed (relevant for all applied for intended uses; data gap identified by EFSA after the expert meeting; no submission date proposed; refer to section 2.12).

The applicant should provide evidence that the submitted residues trials fully cover the residue definition for risk assessment in particular with regard to conjugates. It should be demonstrated that the method used would extract all the conjugate and that the hydrolysis step in the method gives an acceptable yield (relevant for all representative uses evaluated; data gap confirmed as still outstanding after the resubmission application; no submission date proposed by the applicant; data gap identified by the meeting of experts, refer to section 3.1.1).

The exposure of the consumer to triazole metabolites to be addressed for crops (grapes) in following growing seasons (relevant for all representative uses evaluated; no submission date proposed by the applicant; data gap confirmed as still outstanding after the resubmission application; refer to section 3.1.2).

Information is required as to whether significant uptake of myclobutanil into the crop (grapes) can be expected in following growing seasons and upon continuous use of myclobutanil and may have an impact on the final residue levels (relevant for all representative uses evaluated; no submission date proposed by the applicant; data gap confirmed as still outstanding after the resubmission application; refer to section 3.1.2).

The applicant should address the consumer risk assessment with regard to the two myclobutanil isomers (relevant for all representative uses evaluated; no submission date proposed by the applicant; data gap identified by the meeting of experts, refer to section 3.3).

Impact of different isomer ratios on the environmental risk assessment of myclobutanil is to be addressed (relevant for the representative use; data gap confirmed as still outstanding after the resubmission application; no submission date proposed; refer to sections 4 and 5).

CONCLUSIONS AND RECOMMENDATIONS

OVERALL CONCLUSIONS

The conclusion was reached on the basis of the evaluation of the representative uses as proposed by the applicant which comprise foliar spraying against powdery mildew (*Uncinula necator)*, and black rot *(Guignardia bidwelli)* in table and wine grapes, in all EU countries, up to a maximum four applications at a maximum individual application rate per spray of 48 g a.s./ha, with an interval of 10 days between applications.

The representative formulated product for the evaluation was 'Systhane 20 EW', an oil in water emulsion (EW) containing 200 g/l myclobutanil, registered under different trade names in Europe.

Adequate analytical methods are available to monitor all compounds given in the respective residue definitions.

Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection products are possible.

In mammalian toxicity tests, myclobutanil is harmful if swallowed, it is not toxic via dermal and inhalation routes, and it is not a skin irritant or a skin sensitiser. The ECB has classified myclobutanil with R36 ("Irritating to eyes"). The overall subchronic NOAEL is 3.09 mg/kg bw/day. Myclobutanil does not show any genotoxic or carcinogenic potential. The relevant NOAEL for long-term toxicity is 2.5 mg/kg bw/day. The relevant parental, offspring and reproductive NOAEL is 16 mg/kg bw/day. Myclobutanil is classified as Repr. Cat 3, R63 ("Possible risk of harm to the unborn child"). The relevant parental NOAEL is 94 mg/kg bw/day, while the relevant developmental NOAEL is 31 mg/kg bw/day. No indication of any other neurological effects was found in the toxicological studies. The ADI is 0.025 mg/kg bw/day, the AOEL 0.03 mg/kg bw/day and the ARfD is 0.31 mg/kg bw. The operator, worker and bystander exposure estimates showed levels below the AOEL.

The metabolism of myclobutanil was investigated in grapes (representative use), apples and additionally in wheat. In grapes and apples at harvest, the major components of the residue were myclobutanil and its metabolite RH-9090[19] in free and conjugated form. A metabolic cleavage of the myclobutanil molecule which would generate triazole derivative metabolites was - in contrast to the wheat study - not observed in apples and grapes at the investigated pre harvest intervals. Based on the available plant metabolism data for the categories fruit and cereals it was concluded that the metabolism is not comparable amongst different crop groups. As for the representative uses, however, it was agreed that the relevant residue for the category fruit crops should be defined as myclobutanil and its metabolite RH-9090 (free and conjugated). A sufficient number of residue trials in grapes are available; however, there is still evidence required that the submitted trials fully cover the proposed residue definition and conjugates were determined with an acceptable yield. In processing studies it was investigated how the residue levels of myclobutanil and metabolite RH-9090 change when grapes are processed to juice, wine, etc. It was further demonstrated in a hydrolysis study that both myclobutanil and metabolite RH-9090 are likely to remain stable under processing conditions.

The investigation of residues in rotational and succeeding crops was considered not relevant since both apples and grapes are perennial crops that are usually not grown in rotation with other crops. However it was highlighted that upon repeated application and in the long term the issue of potential uptake of myclobutabil residues and/or triazole derivative metabolites could become relevant. The issue of triazole derivative metabolites might have to be followed up separately as this concern is not specific to the active substance myclobutanil alone but common to a number of triazole pesticides.

Moreover, the risk assessment with regard to the two isomers of myclobutanil was not addressed.

As a consequence of the identified data gaps, the consumer risk assessment for the representative use on grapes was not fully finalised.

It is also noted that the consumer could be exposed to residues of myclobutanil butyric acid,[20] which may occur in groundwater above 0.75µg/L (up to 0.81675µg/L) for which the mammalian toxicology assessment indicates the ADI for parent myclobutanil could be used. Therefore, in addition to exposure from residues in food an exposure of consumers can be expected when ground water is used as drinking water though this route of exposure is not considered significant (<1% ADI and ARfD).

The information available on the fate and behaviour in the environment is generally sufficient to carry out an appropriate environmental exposure assessment at the EU level for total myclobutanil isomers. A laboratory anaerobic soil degradation study was identified as being necessary to support the applied

[19] RH-9090: (2*RS*,5*RS*) 2-(4-chlorophenyl)-5-hydroxy-2-(1*H*-1,2,4-triazol-1-ylmethyl)hexanenitrile
[20] myclobutanil butyric acid: (3*RS*) 3-(4-chlorophenyl)-3-cyano-4-(1*H*-1,2,4-triazol-1-yl)butanoic acid

for intended use on apples in territories where anaerobic soil conditions occur and coincide with apple growing areas. On the basis of the available reliable information, it cannot be excluded that for the original representative use on apples, there is no concern for groundwater exposure by myclobutanil and myclobutanil butyric acid above the parametric drinking water limit of 0.1 µg/L over a wide range of European geoclimatic conditions. However based on the information in the resubmission application, it was possible to conclude that for the representative use assessed on grapes, the potential for groundwater exposure by myclobutanil above the parametric drinking water limit of 0.1 µg/L was low in geoclimatic situation represented by 6 out of the 7 pertinent FOCUS groundwater scenarios. In situations represented by the Piacenza scenario there is a potential for contamination (the estimated concentration was 0.21 µg/L). For the metabolite myclobutanil butyric acid, groundwater exposure above the parametric drinking water limit of 0.1 µg/L might be expected in situations represented by all 7 FOCUS groundwater scenarios, parameterised for grape vines. Concentrations > 0.75 µg/L (a key assessment trigger from the groundwater metabolite relevance guidance document) was estimated in situations represented by the FOCUS Hamburg vine scenario (estimated concentrations being up to 0.816 µg/L). A groundwater metabolite non relevance assessment was therefore necessary for myclobutanil butyric acid. This assessment was made available in the resubmission application. The conclusion of this assessment was that this metabolite could be considered not relevant.

The risk to birds, mammals, aquatic organisms, bees, non-target arthropods, earthworms, other soil non-target macro-organisms, soil non-target micro-organisms, non-target plants and biological methods of sewage treatment was assessed as low for the respresentative use in vineyards. It was identified that the risk assessment did not address the potential for different myclobutanil isomer ratios to be present in the environment.

PARTICULAR CONDITIONS PROPOSED TO BE TAKEN INTO ACCOUNT TO MANAGE THE RISK(S) IDENTIFIED

none

ISSUES THAT COULD NOT BE FINALISED

There are a number of uncertainties identified in the estimation of the nature and level of residues in grapes. The consumer risk assessment cannot be finalised as it is currently unclear whether the available residue data do fully cover all compounds of the residue definition for risk assessment and whether significant uptake of myclobutanil into grapes can be expected in following growing seasons and upon continuous use of myclobutanil and may have an impact on the final residue levels. The consumer exposure and risk assessment is also not sufficiently addressed with regard to the triazole derivative metabolites and the two isomers of myclobutanil. Data gaps need however to be addressed in order to finalise the risk assessment and to confirm that the toxicological reference values are effectively not exceeded.

CRITICAL AREAS OF CONCERN

none

REFERENCES

Belgium, 2007. Draft Assessment Report (DAR) on the active substance myclobutanil, prepared by the rapporteur Member State Belgium in the framework of Directive 91/414/EEC, July 2007.

Belgium, 2009. Additional Report to the Draft Assessment Report on the active substance myclobutanil, prepared by the rapporteur Member State Belgium in the framework of Commission Regulation (EC) No 33/2008, September 2009

Belgium 2010, Final Addendum to the Additional Report on myclobutanil, compiled by EFSA, April 2010.

EFSA (European Food Safety Authority), 2009, Conclusion regarding the peer review of the pesticide risk assessment of the active substance myclobutanil; EFSA Scientific Report (2009) 289.

EFSA (European Food Safety Authority), 2010. Peer Review Report to the conclusion regarding the peer review of the pesticide risk assessment of the active substance myclobutanil;

EFSA 2010. Conclusion regarding the peer review of the pesticide risk assessment of the active substance myclobutanil; EFSA Scientific Report (2010) 1682.

Guidance documents[21]:

EFSA, 2009. Guidance of EFSA; Risk Assessment for Birds and Mammals on request from EFSA. EFSA Journal 2009; 7(12): 1438

European Commission, 2003. Guidance document on assessment of the relevance of metabolites in groundwater of substances regulated under council directive 91/414/EEC. SANCO/221/2000-rev 10-final, 25 February 2003.

FOCUS (2006) "Guidance Document on Estimating Persistence and Degradation Kinetics from Environmental Fate Studies on Pesticides in EU Registration" Report of the FOCUS Work Group on Degradation Kinetics, EC Document Reference Sanco/10058/2005 version 2.0, 434 pp

EFSA (2007a), Opinion on a request from EFSA related to the default Q10 value used to describe the temperature effect on transformation rates of pesticides in soil Scientific Opinion of the Panel on Plant Protection Products and their residues: The EFSA Journal (2007) 622, 1-32.EFSA (2007).

EFSA (2007b) Opinion of the Scientific Panel on Plant protection products and their Residues on a request from the Commission related to the revision of Annexes II and III to Council Directive 91/414/EEC concerning the placing of plant protection products on the market - Fate and Behaviour in the Environment: The EFSA Journal (2007) 448, 1-17.

EFSA (2004). Opinion of the Scientific Panel on Plant Health, Plant Protection Products and their Residues on a request of EFSA related to FOCUS groundwater models comparability and the consistency of this risk assessment of groundwater contamination. The EFSA Journal (2004) 93, 1-20

PHED (1998). PHED Surrogate Exposure Guide. Estimates of Worker Exposure from The Pesticide Handler Exposure Database. Version 1.1, August 1998.

[21] For further guidance documents see http://ec.europa.eu/food/plant/protection/resources/publications_en.htm#council (EC) or http://www.oecd.org/document/59/0,3343,en_2649_34383_1916347_1_1_1_1,00.html (OECD)

APPENDICES

APPENDIX A – LIST OF END POINTS FOR THE ACTIVE SUBSTANCE AND THE REPRESENTATIVE FORMULATION

(Abbreviations used in this list are explained in appendix B)

Added in October 2009:
The following list of end points is an amended version of the list of end points that was included in the EFSA conclusion dated 4 June 2009 (EFSA Scientific Report (2009) 298, 1-97). Changes made as a result of the assessment of new data provided in the resubmission dossier (2009) are highlighted in yellow.

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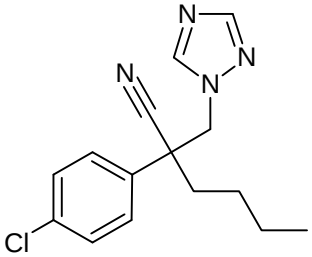
Identity, Physical and Chemical Properties, Details of Uses, Further Information

Active substance (ISO Common Name) ‡	Myclobutanil
Function (*e.g.* fungicide)	Fungicide
Rapporteur Member State	Belgium

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	(*RS*)-2-(4-chlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)hexanenitrile
Chemical name (CA) ‡	α-butyl-α-(4-chlorophenyl)-1*H*-1,2,4-triazole-1-propanenitrile
CIPAC No ‡	442
CAS No ‡	88671-89-0
EEC No (EINECS or ELINCS) ‡	410-400-0
FAO Specification (including year of publication)‡	No FAO specification exists for myclobutanil
Minimum purity of the active substance as manufactured (g/kg) ‡	925 g/kg (industrial scale production) (racemic mixture, i.e. ratio of R/S-isomers = 1:1)
Identity of relevant impurities (of toxicological, environmental and/or other significance) in the active substance as manufactured (g/kg)	1-methylpyrrolidin-2-one max. 1 g/kg
Molecular formula ‡	$C_{15}H_{17}ClN_4$
Molecular mass ‡	288.8 u
Structural formula ‡	

Physical-chemical properties (Annex IIA, point 2)

Melting point (state purity) ‡	70.9 °C (98.75%)
Boiling point (state purity) ‡	390.8 °C (98.75%)
Temperature of decomposition (state purity)	Not applicable (melting point and boiling point could be determined)
Appearance (state purity) ‡	white crystals, odourless (98.75%); colourless to white crystals, faint aldehyde odour (95.4%)
Vapour pressure (state temperature, state purity) ‡	1.98 x 10^{-4} Pa at 20°C (99.9%)
Henry's law constant (Pa m^3 mol^{-1}) ‡	4.33 x 10^{-4} $Pa.m^3.mol^{-1}$ at 20°C (99.9%)
Solubility in water (state temperature, state purity and pH) ‡	pH 3-5, 20°C : 124 mg/L (99.9%)
	pH 7, 20°C : 132 mg/L (99.9%)
	pH 9-11, 20°C : 115 mg/L (99.9%)
Solubility in organic solvents (state temperature, state purity) ‡	

	at 20°C in g/L (95.6%)
n-heptane	1.02
xylene	270
1,2-dichloroethane	> 250
methanol	> 250
n-octanol	102
acetone	> 250
ethyl acetate	> 250

Surface tension (state concentration and temperature, state purity)‡	46.8 mN/m at 24°C (90% saturated solution) (92.1%)
Partition co-efficient (state temperature, pH and purity) ‡	log Pow = 2.89 (calculated; pH 7, 20°C); log Pow = 3.5 (estimation); log Pow = 3.17 (experimental - shake flask method; 20°C, pH 4,7,9) (99.7%)
	Effect of pH does not need to be addressed (molecule will not be ionized at environmentally relevant pH values)
Dissociation constant (state purity) ‡	Myclobutanil is calculated to have a basic pKa of 2.30 ± 0.10 This indicates that the molecule will not be ionized at environmentally relevant pH values.
UV/VIS absorption (max.) incl. ε (state purity, pH) ‡	in unbuffered methanol (98.75%): λ_{max} 203 nm; ε = 16400 $L.mol^{-1}.cm^{-1}$ λ_{max} 219 nm; ε = 17900 $L.mol^{-1}.cm^{-1}$ λ_{max} 267 nm; ε = 500 $L.mol^{-1}.cm^{-1}$ λ_{max} 273 nm; ε = 500 $L.mol^{-1}.cm^{-1}$ at λ ≥ 290 nm : ε = 0 $L.mol^{-1}.cm^{-1}$
Flammability (state purity) ‡	not highly flammable; not flammable in contact with water or damp air (92.1%) not auto-flammable (92.1%)
Explosive properties (state purity) ‡	not explosive (95.6%)

Oxidising properties (state purity) ‡	not oxidising (95.6%)

Summary of representative uses evaluated (Myclobutanil)*

Crop and/or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of a.s. (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hl min max	water l/ha min max	kg as/ha min max		
Table/wine Grapes FB0269	N & S Europe	Systhane 20 EW (GF-1317)	F	Powdery Mildew (*Uncinula necator)* and black rot *(Guignardia bidwelli)*	EW	200	Air-assisted spraying	Fruit development	3 - 4 *	10	0.003-0.0048	1000	0.03-0.048	14	~~[1]~~

In the resubmission dossier, the applicant proposed to change the number of applications for the use in grapes to a range of 3 – 4 applications (instead of 4), arguing that this would reflect better the actual use in various geographies. This minor change in the intended GAP is accepted, as the maximum number of applications remains unchanged (at 4 applications/treatment) and hence, the risk assessment performed is not affected.

Remarks:
(a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)
(b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
(f) All abbreviations used must be explained
(g) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting,
(i) g/kg or g/l
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) The minimum and maximum number of application possible under practical conditions of use must be provided

* Uses for which the risk assessment cannot be concluded are marked grey.

(h) drench
Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated

(l) PHI - minimum pre-harvest interval
(m) Remarks may include: Extent of use/economic importance/restrictions

Methods of Analysis

Analytical methods for the active substance (Annex IIA, point 4.1)

Technical as (analytical technique)	GC-FID conf. by MS no CIPAC method available
Impurities in technical as (analytical technique)	GC-FID conf. by MS
Plant protection product (analytical technique)	GC-FID conf. by column of different polarity no CIPAC method available

Analytical methods for residues (Annex IIA, point 4.2)

Food/feed of plant origin (analytical technique and LOQ for methods for monitoring purposes)	Multi-method EN 15662:2008 (QuEChERS): LC-MS(/MS); myclobutanil; LOQ = 0.025 mg/kg (acidic matrices)
Food/feed of animal origin (analytical technique and LOQ for methods for monitoring purposes)	Multi method DFG S19 (extended revision): GC-ECD, conf. by column of different polarity; metabolite RH-9090; LOQ = 0.01 mg/kg (milk, meat, kidney, liver); ILV available Single method ER 58.13: GC-ECD, conf. by GC-NPD; metabolite RH-9090; LOQ = 0.01 mg/kg (fat); ILV available (method ref. ER 59.6)
Soil (analytical technique and LOQ)	Multi method DFG S19 (extended revision) : GC-ECD, conf. by column of different polarity (Myclobutanil); LOQ = 0.05 mg/kg
Water (analytical technique and LOQ)	Single method GRM 03.14 : LC-MS/MS (Myclobutanil); LOQ = 0.05 µg/L (surface water, groundwater, drinking water)
Air (analytical technique and LOQ)	Single method: HPLC-MS-MS; LOQ ≈ 0.7 µg/m³.
Body fluids and tissues (analytical technique and LOQ)	Not required (active substance is not classified as toxic or highly toxic).

Classification and proposed labelling (Annex IIA, point 10)

with regard to physical/chemical data	none

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Impact on Human and Animal Health

Absorption, distribution, excretion and metabolism in mammals (Annex IIA, point 5.1)

Rate and extent of absorption ‡	Rapid and extensive (100% within 96 h) after low dose application
Distribution ‡	Widely distributed; highest levels in liver, kidneys, intestine and adrenals
Potential for accumulation‡	No evidence of accumulation
Rate and extent of excretion ‡	>80% within 96 h evenly divided between urine (35-48%) and faeces (31-44%)
Metabolism in animals ‡	Extensive metabolism in rats (low level of parent compound in urine and faeces) by oxidation of the butyl side chain; no cleavage of the molecule.
Toxicologically significant compounds (animals, plants) ‡	Myclobutanil and metabolites (RH-9089, RH-9090)
Toxicologically significant compounds (environment) ‡	Myclobutanil

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral ‡	Male = 1600 mg/kg bw **Xn, R22** Female = 2290 mg/kg bw
Rat LD_{50} dermal ‡	> 2000 mg/kg bw
Rat LC_{50} inhalation ‡	>5.1 mg/L 4 h, nose only, highest obtainable concentration
Skin irritation ‡	Non-irritant
Eye irritation ‡	Non irritating (according to available information), but already classified at ECB **Xi, R36**
Skin sensitization (test method used and result) ‡	Non-sensitiser (Maximisation test)

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect ‡	Liver
Lowest relevant oral NOAEL / NOEL ‡	3.09 mg/kg bw/day. (90 d and 1 y dog)
Lowest relevant dermal NOAEL / NOEL ‡	100 mg/kg bw/d (4 wk rat)
Lowest relevant inhalation NOAEL / NOEL ‡	No data- not required

Genotoxicity (Annex IIA, point 5.4) ‡	No genotoxic potential

Long term toxicity and carcinogenicity (Annex IIA, point 5.5)

Target/critical effect ‡	Testes (atrophy, oligospermatogenesis) (rats); liver (mice)

Lowest relevant NOAEL / NOEL ‡	2.5 mg/kg bw/d (rat)
Carcinogenicity ‡	No carcinogenic potential

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction target / critical effect ‡	Parental: slight body weight reduction and liver effects
	Offspring: decreased weight gain of pups during lactation
	Reproduction: Reduced number females delivering litters; increased incidence of still-born pups; at slight parental toxic dose
Lowest relevant NOAEL / NOEL ‡	Parental: 16 mg/kg bw/d
	Offspring: 16 mg/kg bw/d
	Reproductive: 16 mg/kg bw/d
Developmental target / critical effect ‡	Altered viability index without maternal toxicity **Repro.Cat 3, R63**
‡ Lowest relevant developmental NOAEL / NOEL	31 mg/kg bw/d (rat study)
Lowest relevant maternal NOAEL / NOEL	94 mg/kg bw/day, (rat study) Clinical signs

Neurotoxicity / Delayed neurotoxicity (Annex IIA, point 5.7) ‡

No data, not required

.

Other toxicological studies (Annex IIA, point 5.8) ‡

Parent compound: Slight inducer of xenobiotic metabolising enzymes. Not an inducer of peroxisomal proliferation Metabolites and impurities: RH-9090 and RH9089 (plant metabolites): 300 mg/kg bw <LD50oral<1000mg/kg bw Impurities: RH-8812: 300 mg/kg bw <LD50oral<1000mg/kg bw RH-8813: LD50 oral > 3000 mg/kg bw Butyric Acid (X11292885) (soil metabolite): *In Vitro* genotoxicity studies: Ames Test: Negative CHO/HGPRT Assay: negative RLCAT: Equivocal *In Vivo* genotoxicity studies: Mouse Micronucleus test: Negative Developmental Toxicity Studies: Maternal NOEL>450mg/kg Developmental NOEL: >450mg/kg

Medical data (Annex IIA, point 5.9) ‡

No detrimental effects on health in manufacturing personnel

Summary (Annex IIA, point 5.10)

	Value	Study	Safety factor
ADI ‡	0.025 mg/kg bw/day	Rat, 2 y study	100
AOEL ‡	0.03 mg/kg bw/d	90 d & 1y, dog study	100
ARfD (acute reference dose) ‡	0.31 mg/kg bw	Developmental rat study	100

Dermal absorption (Annex IIIA, point 7.3) ‡

Systhane 20 EW	25% for concentrate and 15% for diluted from an in vivo rat study & comparative human/rat skin study with Systhane 20 EW

Acceptable exposure scenarios (including method of calculation)

Operator	UK POEM: tractor mounted /trailed broadcast air assisted sprayer, 500L; wine grape: 77% of AOEL (no PPE) German Model: wine grape: 74%
Workers	32% of AOEL (no PPE)
Bystanders	0.15% of AOEL

Classification and proposed labelling (Annex IIA, point 10)

With regard to toxicological data	Xn; R22 Repr. Cat 3; R63 R22: Harmful if swallowed R36: Irritating to eyes R63: Possible risk of harm to the unborn child

Revised in February 2010

Residues

Metabolism in plants (Annex IIA, point 6.1 and 6.7, Annex IIIA, point 8.1 and 8.6)

Plant groups covered	Fruit (Table and wine grapes - representative use). A metabolism study in wheat (not supported use) was available.
Rotational crops	Studies not required for perennial crops.
Metabolism in rotational crops similar to metabolism in primary crops?	Not applicable
Processed commodities	A processing study to determine the nature of the residues of Myclobutanil in processed commodities was provided. Myclobutanil and its metabolite RH-9090 can be regarded as stable to hydrolysis conditions simulating the processing practices.
Residue pattern in processed commodities similar to residue pattern in raw commodities?	Yes.
Plant residue definition for monitoring	Myclobutanil (for fruit, foliar application only)
Plant residue definition for risk assessment	Myclobutanil + RH-9090, free and conjugated expressed as myclobutanil equivalents (for fruit, foliar application only)
Conversion factor (monitoring to risk assessment)	Not relevant. Supervised residue trials were provided to determine the residues of Myclobutanil and RH-9090. Whether conjugates of metabolite RH 9090 were determined with an acceptable yield (efficiency of the hydrolysis step was not demonstrated) in the residue trials could not be clarified.

Metabolism in livestock (Annex IIA, point 6.2 and 6.7, Annex IIIA, point 8.1 and 8.6)

Animals covered	A new ruminant metabolism study is not required according to the representative use on grapes. A metabolism study in laying hens is available but not required.
Time needed to reach a plateau concentration in milk and eggs	Unable to conclude
Animal residue definition for monitoring	Not required.
Animal residue definition for risk assessment	Not required.
Conversion factor (monitoring to risk assessment)	Not relevant
Metabolism in rat and ruminant similar (yes/no)	Unable to conclude based on the available data.
Fat soluble residue: (yes/no)	Yes (log P*o/w* myclobutanil 3.17 at room temperature)

Residues in succeeding crops (Annex IIA, point 6.6, Annex IIIA, point 8.5)

.....	Not required. Vines is a long-lived crop that is not grown in rotation

with other succeeding crops. Use is only acceptable for permanent crops as rotational crops are not addressed by data. The potentially minor soil metabolite 1,2,4-triazole was not detected in soil above the trigger value applied in the F&B studies, and it degrades relatively quickly compared to myclobutanil (Lab DT50 potential soil metabolite 1,2,4-triazole: 6-12 days). However, it cannot be excluded that it will be formed long term from continuous use of Myclobutanil and there may be uptake and accumulation of the TDMs. Due to the high persistency of Myclobutanil in soil, further information as to whether significant uptake of Myclobutanil into grapes can be expected in following growing seasons and upon continuous use of Myclobutanil that may have an impact on the final residue levels is required.

Stability of residues (Annex IIA, point 6 introduction, Annex IIIA, point 8 introduction)

For all the studies submitted, the recovery values were generally acceptable for myclobutanil and its metabolites (RH-9090 and RH-0294) except for almond hulls and meat at 24 months. -Residues of myclobutanil can be considered as stable in apples and grapes for a minimum of 24 months under frozen storage conditions (–15°C) as no significant residue degradation occurred during storage. The stability of the metabolite RH-9090 and its conjugates was not investigated in this study. -Residues of myclobutanil and its metabolite RH-9090 are considered as stable in muscle and liver for up to 80 days under frozen storage conditions at –10°C. -Residues of the metabolite RH-0294 are considered as stable in milk for up to 15 months under frozen storage conditions at –10°C. -Residues of myclobutanil and its metabolite RH-9090 in almond meat and hulls are stable for 18 months at –10°C. To be noted that radio validation of the extraction procedure for the analytical method TR 34S-88-10 was provided only for apples (high water matrix) and grapes samples (high acid matrix) but not in high oil content matrices-see point B.7.6 in the revised DAR. -Residues of myclobutanil and its metabolite RH-9090 in cucumbers are stable for up to 36 months at –10°C. The radio validation of the extraction procedure for the analytical method TR 34S-88-10 was provided for high water content matrices - see point B.7.6 in the revised DAR. -Residues of myclobutanil and its metabolite RH-9090 in tomatoes are stable for up to 36 months at –10°C. The radio validation of the extraction procedure for the analytical method TR 34S-88-10 was provided for high water content matrices- see point B.7.6 in the revised DAR.

Residues from livestock feeding studies (Annex IIA, point 6.4, Annex IIIA, point 8.3)

	Ruminant:	Poultry:	Pig:
	Conditions of requirement of feeding studies		
Expected intakes by livestock ≥ 0.1 mg/kg diet (dry weight basis) (yes/no - If yes, specify the level)	N/A	N/A	N/A
Potential for accumulation (yes/no):	N/A	N/A	N/A
Metabolism studies indicate potential level of residues ≥ 0.01 mg/kg in edible tissues (yes/no)	N/A	N/A	N/A
	Feeding studies (Specify the feeding rate in cattle and poultry studies considered as relevant) Residue levels of Myclobutanil in matrices : Mean (max) mg/kg		
Feeding rate in cattle and poultry studies	-1.6 mg/kg in total diet (low treatment level) -16 mg/kg (high treatment level)	No feeding study required.	No feeding study required.
Muscle	N/A	N/A	N/A
Liver	N/A	N/A	N/A
Kidney	N/A	N/A	N/A
Fat	N/A	N/A	N/A
Milk	N/A	-	-
Eggs	-	N/A	-

Summary of residues data according to the representative uses on raw agricultural commodities and feedingstuffs (Annex IIA, point 6.3, Annex IIIA, point 8.2)

Crop	Northern or Southern Region	Trials results relevant to the critical GAP (a)	Recommendation/comments	**MRL** estimated from trials according to representative use	**STMR** (b)
Grapes	North Europe	**-Myclobutanil:** **Method *310-84-13*:**0.29-0.41-0.33-0.28-0.16-0.51 mg/kg **Method *DMK/03/1*:** 0.07-0.05-0.1-0.07-0.14-0.06-0.08-0.1 mg/kg **-RH 9090 expressed as Myclobutanil equiv.:** **Method *310-84-13*:**0.02-0.02-0.02-0.03-0.02-0.03 mg/kg **Method *DMK/03/1*:** 0.01-<0.01-0.02-0.01-0.02-<0.01-0.01-<0.01 mg/kg	The residue trials were carried out at a dosing rate ranging between 0.012 and 0.060 kg a.s./ha, 8 applications, BBCH 81-85 (fruit ripening), PHI : 0-28 days. A distinction was made between the residue data generated by the analytical method 310-84-13 (the extraction procedure does not include a hydrolysis step) and the residue data generated by analytical method DMK/03/1 (the extraction procedure includes an acidic (not validated) hydrolysis step) **Data gap:** It should be demonstrated the method used would extract all conjugates and that the hydrolysis step gives an acceptable yield.	1 mg/kg	0.14
	South Europe	**-Myclobutanil:** **Method *310-84-13*:**0.03-0.09-0.04-0.1-0.13 mg/kg **Method *DMK/03/1*:** 0.02-0.06-0.03-0.02-0.09-0.1-0.03-0.02-0.08 mg/kg **-RH 9090 expressed as Myclobutanil equiv.:** **Method *310-84-13*:**<0.01-0.01-<0.01-0.01-0.01 mg/kg **Method *DMK/03/1*:**<0.01-<0.01-<0.01-<0.01-0.02-0.02-<0.01-<0.01-0.03 mg/kg	26 on the 42 trials on grapes were analysed according to the analytical method *310-84-13*. The extraction procedure of this method did not include a hydrolysis step. 16 trials on grapes were performed and analysed according to the method *DMK/03/1*. This method involved extraction with methanol followed by acidic hydrolysis to free any conjugated RH-9090. Radiovalidation was provided for a different analytical method *TR 34S-88-10*, but, it is unclear whether the results of the radiovalidation demonstrating the efficiency of the extraction and the acid hydrolysis steps of the method *TR 34S-88-10* are also valid for the method *DMK/03/1* since the extraction procedures of the 2 methods are different. **Data gap:** It should be demonstrated the method used would extract all conjugates and that the hydrolysis step gives an acceptable yield.		0.06

(a) Numbers of trials in which particular residue levels were reported *e.g.* 3 x <0.01, 1 x 0.01, 6 x 0.02, 1 x 0.04, 1 x 0.08, 2 x 0.1, 2 x 0.15, 1 x 0.17
(b) Supervised Trials Median Residue *i.e.* the median residue level estimated on the basis of supervised trials relating to the critical GAP

Consumer risk assessment (Annex IIA, point 6.9, Annex IIIA, point 8.8)

a) For myclobutanil and RH-9090, free and conjugated:

(1) uncertainty in terms of the total amounts of metabolite RH 9090 (free and conjugated): the extraction procedure of the analytical method *310-84-13* did not include a hydrolysis step and the radio validation of the analytical method *DMK/03/1*was not addressed
(2) risk assessment not addressed with regard to the myclobutanil isomers
(3) uncertainty whether upon continuous use myclobutanil could be taken up in the following season's crop and may have an impact on the final residue levels

ADI	0.025 mg/kg b.w./day
TMDI (% ADI) according to WHO European diet	The consumer risk assessment cannot be considered as finalised due to the different identified uncertainties. Provisional assessment :
TMDI (% ADI) according to national (to be specified) diets (EFSA PRIMo rev. 2a)	The consumer risk assessment cannot be considered as finalised due to the different identified uncertainties. Provisional assessment, uncertain: 16% ADI (FR all population); all other diets use less
IEDI (WHO European Diet) (% ADI)	Not calculated
NEDI (specify diet) (% ADI)	n/a
Factors included in IEDI and NEDI	n/a
ARfD	0.31 mg/kg b.w/day
IESTI (% ARfD) according to EFSA PRIMo rev. 2a	The consumer risk assessment cannot be considered as finalised due to the different identified uncertainties. Provisional assessment, uncertain: 21 % ARfD for table grapes; all other diets use less
NESTI (% ARfD) according to national (to be specified) large portion consumption data	Not calculated
Factors included in IESTI and NESTI	n/a

b) For triazole derivative metabolites:

The triazole derivate metabolites were not recovered in the fruit crops following foliar application of Myclobutanil, but should be addressed for grapes)in following growing seasons

c) Drinking water risk assessment

Note: There might be additional consumer exposure through drinking water due to the myclobutanil butyric acid metabolite leaching to ground water at significant levels. Negligible contribution to the consumers 'acute and chronic exposure might be expected when ground water is used as drinking water (<1% ADI and ARfD).

Processing factors (Annex IIA, point 6.5, Annex IIIA, point 8.4)

Residue trial references	RAC/Processed commodities	Myclobutanil/RH-9090 residues in whole fruit	Myclobutanil /RH-9090 residues in processed fractions	Transfer factors (RAC/processed fraction) for myclobutanil	% of transference
Grapes					
Trial N°RH/203/2/G[(1)]	**Unwashed whole white grapes**	0.41/0.02	na		
	Juice	na	0.09/<0.01	*0.219*	*15.33*
	Young wine	na	0.06/<0.01	*0.146*	*2.90*
	Mature wine	na	0.07/<0.01	*0.170*	
Trial N°RH/203/3/G[(1)]	**Unwashed whole red grapes**	0.34/0.015	na		
	Juice	na	0.07/<0.01	*0.205*	
	Young wine	na	0.04/<0.01	*0.117*	
	Mature wine	na	0.04/<0.01	*0.117*	
Trial N°RAS/18/4/F[(1)]	**Unwashed whole red grapes**	0.51/0.03	na		
	Juice	na	0.08/0.01	*0.156*	*10.16*
	Young wine	na	0.04/0.01	*0.078*	*3.08*
	Mature wine	na	0.05/0.02	*0.098*	

Na : not applicable
- : Material balance not available.
RAC : Raw agricultural commodity.
Limit of Quantification for all the processed commodities : 0.01 mg/kg.
Remark :
Grapes : no data were provided on raisins.
(1): The residues of Myclobutanil and its metabolite RH-9090 were determined according to the analytical method *310-84-13* that did not include a hydrolysis step to release the RH-9090 conjugates, i.e. uncertainty in terms of the total amounts of metabolite RH 9090 (free and conjugated).

Proposed MRLs (Annex IIA, point 6.7, Annex IIIA, point 8.6)

Grapes	1 mg/kg

When the MRL is proposed at the LOQ, this should be annotated by an asterisk after the figure

Fate and Behaviour in the Environment

Route of degradation (aerobic) in soil (Annex IIA, point 7.1.1.1.1)

Mineralization after 100 days ‡	0.2-1.6 % after 120 d, [^{14}C-triazole]-label (n= 3) 1.7 % after 120 d, [^{14}C-chlorophenyl]-label (n= 1) Sterile conditions: no acceptable study, not required
Non-extractable residues after 100 days ‡	4.1-15.9 % after 120 d, [^{14}C-triazole]-label (n= 3) 8.0 % after 120 d, [^{14}C-chlorophenyl]-label (n= 1) Sterile conditions: no acceptable study, not required
Relevant metabolites - name and/or code, % of applied (range and maximum) ‡	No major metabolite Minor metabolite myclobutanil butyric acid (max 6%AR at 76 days) Though this "butyric acid" metabolite only reached a max 6% AR, for FOCUS gw modelling, the consequent associated kinetic formation fraction of 0.6 was estimated from the FOCUS kinetics modelling to generate the mass represented by 6%AR that was the measured formation mass.

Route of degradation in soil - Supplemental studies (Annex IIA, point 7.1.1.1.2)

Anaerobic degradation ‡	No acceptable study, not required for the use on grape vines.
Soil photolysis ‡	No satisfactory study available. Not required due to the low light absorbance of the myclobutanil molecule > 290nm.

Rate of degradation in soil (Annex IIA, point 7.1.1.2, Annex IIIA, point 9.1.1)

Method of calculation	Laboratory: Parent and metabolite according to FOCUS kinetics guidance, 2006. SFO, standardised to 20°C(Q_{10} 2.58)/pF2. Field studies: Parent only according to FOCUS kinetics guidance, 2006. DFOP (DT_{50} calculated from the slower phase of the DFOP model.), standardised to 20°C(Q_{10} 2.58) only for FOCUS simulation modelling.
Laboratory studies (range or median, with n value, with r^2 value) ‡	Myclobutanil DT_{50lab} (aerobic): 20°C 40%MWHC: 191, 369, 464 & 1216 days (SFO) 22°C unknown %MWHC: 191, 216 & 354 days (SFO)chi^2 1.9-7.9% For FOCUS gw and sw modelling: 149, 163, 231, 287, 331, 417 &1092 d, (SFO) geomean 305 d (standardised to 20°C(Q_{10} 2.58)/pF2).

Myclobutanil DT_{90lab} (aerobic): Not calculated (>1 year, n=7)
Myclobutanil butyric acid DT_{50lab} (aerobic): 4.6, 6.9, 21.9 & 41.9 d, mean 18.8 d (SFO, unstandardised), n=4, chi^2 4.2-7.9% (mean 5.5%). For FOCUS gw and sw modelling: 7.4, 9, 26 & 40.4 d, (SFO) geomean 16.2 d (standardised to 20°C(Q_{10} 2.58)/pF2).
myclobutanil butyric acid DT_{90lab} (aerobic): 15.3-139.1 d, mean 62.5 d (unstandardised), n=4, chi^2 4.2-7.9% (mean 5.5%) (from DT_{50lab} x 3.32)
DT_{50lab} (10°C, aerobic): 1107 d (by calculation from mean at 20°C and Q_{10} 2.58)
DT_{50lab} (anaerobic): Study not required for the use on grape vines.
degradation in the saturated zone: not required

1,2,4-triazole	Aerobic conditions							
Soil type (USDA)		pH ($CaCl_2$)	t. °C / % MWHC	DT_{50}/ DT_{90} (d)	f. f. k_{dp}/k_f	DT_{50} (d) 20°C pF2/10kPa	St. (r^2)	Method of calculation
Sandy loam		6.4	20°C / 40 % MWHC	6.32 / 21.0		5.0	0.75	SFO
Loamy sand		5.8	20°C / 40 % MWHC	9.91 / 33.0		9.9	0.81	SFO
Silt loam		6.7	20°C / 40 % MWHC	12.27 / 40.8		8.2	0.95	SFO
Geometric mean						7.4		

Agreed End-point for calculating PEC soil for EU assessments 12 days (Not normalised).
Geomean for FOCUS modelling 7.4 days

Field studies (state location, range or median with n value) ‡	DT_{50f}: Germany, bare soil, 9, 14, 58, 58 d (n= 4, r^2=0..444-0.782) 1st order. Note the pattern of degradation was biphasic but the slow phase commenced after 50% loss. Myclobutanil DT_{50f} (Germany, bare soil): For FOCUS gw modelling at higher tier: 141.5, 157.5, 192.5, 630.1 d, geomean 228 d (n=4) (standardised only to 20°C(Q_{10} 2.58)), calculated from the slower phase of the DFOP model (k2).
	DT_{90f} (Germany, bare soil): >1 year (n=4) (biphasic degradation (DFOP))
Soil accumulation and plateau concentration ‡	Germany, 12 appl. of 0.045 kg a.s./ha during 3 years, bare soil highest concentration of 0.223 mg/kg in the 0-20 cm horizon reached after 2 years application California, 5 appl. of 0.134 kg a.s./ha during 3 years. highest concentration of 0.105 and 0.112 mg/kg in the 0-15 cm horizon during the 2nd and 3rd years; no increase when further applications are made.

Soil adsorption/desorption (Annex IIA, point 7.1.2)

K_{Ff} /K_{oc} ‡ K_d ‡ pH dependence (yes / no) (if yes type of dependence) ‡	Myclobutanil K_{Foc}: parent 225.7-920.0 mL/g (mean 517 mL/g, $^1/_n$= 0.851-0.912 (mean 0.88), 5 soils) K_F: parent 1.464-9.771 (mean 5.027mL/g, 5 soils) No pH dependence *For FOCUS gw modelling – K_{Foc}: parent, mean 517 mL/g, $^1/_n$=0.88.
	Myclobutanil butyric acid K_{Foc}: 5.3-26.7 (mean 13.2, $^1/_n$= 0.82-1.07 (mean 0.95), 5 soils) No pH dependence *For FOCUS gw modelling – K_{foc}: mean 13.2 mL/g, $^1/_n$ = 0.95.

Metabolite 1,2-4 triazole ‡							
Soil Type(USDA)	OC %	Soil pH ($CaCl_2$)	Kd (mL/g)	Koc (mL/g)	K_F (mL/g)	$K_F$oc (mL/g)	1/n
- Silty clay	0.70	8.8			0.833	120	0.897
Clay loam	1.74	6.9			0.748	43	0.827
Sand	0.12	4.8			0.234	202	0.885[1]
Silty clay loam	0.70	7.0			0.722	104	0.922
Sandy loam	0.81	6.9			0.720	89	1.016
Arithmetic mean (of 4 values excluding the very low OC sand that was considered not representative of agricultural soils)					0.756	89	0.9155
pH dependence (yes or no)			No				

Agreed End-point for calculating FOCUS modelling arithmetic mean $K_F$oc of 89 mL/g, 1/n 0.92 excluding results of the sand soil.

Mobility in soil (Annex IIA, point 7.1.3, Annex IIIA, point 9.1.2)

Column leaching ‡	Not required
Aged residues leaching ‡	Not required
Lysimeter/ field leaching studies ‡	Not required

PEC (soil) (Annex IIIA, point 9.1.3)

Parent (no soil metabolites > 10%)

Method of calculation	Active substance DT_{50} (d): 711.5 days (mean of the two values provided for LUFA 2.1 soils from Knoch and Krieger, 2003) Kinetics: 1st order worst case from lab studies.
Application rate	Crop: grapes 50% plant interception: Number of applications: 4 Interval (d): 10 Application rate(s): 48 g as/ha 5 cm soil horizon with a soil bulk density of 1.5 g/mL

$PEC_{(s)}$ (mg/kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial	0.032	0.032	0.126 (conc just after last application)	-
Short term 24h	0.032	0.032	-	-
2d	0.032	0.032		
4d	0.032	0.032		
Long term 7d	0.032	0.032	-	-
28d	0.031	0.031		
50d	0.030	0.031		
100d	0.029	0.030		

Accumulation PEC soil (mg a.s./kg soil)

	Initial PEC for 1 year	Concentration in soil immediately after last application = Initial PEC for 1 year x $(1-e^{-20k}) / (1-e^{-k})$	Plateau average PEC after repeated applications during several years = initial PEC for 1 year / k
Vines	0.128	0.428	0.360

k is 0.693 /DT_{50} (in year)

Route and rate of degradation in water (Annex IIA, point 7.2.1)

Hydrolysis of active substance and relevant metabolites (DT_{50}) (state pH and temperature) ‡	no significant hydrolysis (< 10%) after 5 d, at 50°C, pH 4, 7 and 9
Photolytic degradation of active substance and relevant metabolites ‡	Not required (Molar absorption coefficient for myclobutanil is zero for wavelengths ≥ 290 nm.)
Readily biodegradable (yes/no) ‡	No

	The Biological Oxygen Demand is 7.8, 13.5 and 22.4% of the Theoretical Oxygen Demand at 5, 15 and 28 days, respectively.
Degradation in water/sediment - DT_{50} water ‡ - DT_{90} water ‡	20-4 days (dissipation from water column) 68-14 days (1st order, r^2 = 0.960-0.969, n= 2)
- DT_{50} whole system ‡ - DT_{90} whole system ‡	415-838 days (mean 626 days selected for use in FOCUSsw modelling) 1379-2784 days (1st order, r^2 = 0.769-0.057, n= 2 (values extrapolated significantly beyond the study duration))
Mineralization	0.3 %AR (at 105 d, study end, n= 2)
Non-extractable residues	4.3-9.8% AR (at 105 d, study end, n= 2)
Distribution in water / sediment systems (active substance) ‡	Maximum level of 65.60-84.80 %AR in sediment after 105 days. DT_{50} in sediment equivalent to the DT50 whole system
Distribution in water / sediment systems (metabolites) ‡	Low levels of metabolites were detected in both sediment and water phases (unknown metabolite found at max level of 4.7% AR)

PEC (surface water) (Annex IIIA, point 9.2.3)

Parent Method of calculation	Model(s) used: SWASH, Spray drift calculator, MACRO, PRZM, TOXSWA Calculations from step 1 to 3 Scenarios: Lanna, Brimstone, Vreedepeel, Skousbo, La Jaillière, Thiva, Weiherbach, Porto, Bologna, Roujean Crop:vines (late applications) Geomean $DT_{50lab(soil)}$: 305 d Mean $DT_{50lab(sediment)}$: 1000 d (FOCUS default) $DT_{50(water)}$: 415 d K_{foc}: parent, mean 517 mL/g, $^1/_n$= 0.88. Molecular weight : 288.8 Vapour pressure: 1.98 10^{-4} Pa Water solubility 132 mg/L Q10 2.58
	Vines Application rate: 48 g/ha. (a) No. of applications: 4 at 10 days interval Time of application: first appl. on 15 May (b) No. of applications: 3 at 10 days interval Time of application: first appl. on 15 May (c) No. of applications: 1 Time of application: first appl. on 15 May
Metabolite (myclobutanil butyric acid) Method of calculation	Model(s) used: FOCUS Steps 1-2 calculator Scenarios: N and S Europe, Mar-May and Jun-Sep Crop: vines (late applications) Geomean $DT_{50lab(soil)}$: 16.2 d Mean $DT_{50lab(sediment)}$: 1000 d (FOCUS default) $DT_{50(water)}$: 1000 d (FOCUS default) $DT_{50(water/sediment\ system)}$: 1000 d (FOCUS default)

	K_{foc}: mean 13.2 mL/g, $^1/_n$= 0.95 Molecular weight: 290.8 Water solubility: 132 mg/L (parent value as surrogate)
	Vines application rate: 48 g/ha. (a) No. of applications: 4 at 10 days interval Time of application: first appl. Mar-May
Main routes of entry	Myclobutanil: Drift, drainage, run-off (according to standard FOCUS scenarios) Myclobutanil Butyric acid: Drainage and run-off only

Summary of PEC_{SW} and PEC_{SED} values for myclobutanil (Step 3 minimum default no-spray zones) following use of Systhane 20EW on vines (late application - worst case for spray drift)

Myclobutanil at FOCUS Step 3 – 4 x 48 g as/ha (supported GAP)

Concentration	PEC Values					
	D6 d (3.5 m)	R1 p (6 m)	R1 s (4 m)	R2 s (4 m)	R3 s (4 m)	R4 s (4 m)
(µg/L)						
Max. PECsw	1.018	0.074	0.880	0.666	0.700	1.956
TWA PECsw 21d	0.524	0.065	0.024	0.025	0.025	0.109
(µg/kg dry weight)						
Max. PECsed	2.918	0.525	0.399	0.474	0.269	1.497
TWA PECsed 21d	2.634	0.525	0.173	0.287	0.128	0.651

Myclobutanil at FOCUS Step 3 – 3 x 48 g as/ha

Concentration	PEC Values					
	D6 d (3.5 m)	R1 p (6 m)	R1 s (4 m)	R2 s (4 m)	R3 s (4 m)	R4 s (4 m)
(µg/L)						
Max. PECsw	0.895	0.063	0.559	0.687	0.725	1.229
TWA PECsw 21d	0.516	0.055	0.022	0.026	0.026	0.066
(µg/kg dry weight)						
Max. PECsed	2.534	0.406	0.274	0.475	0.227	0.894
TWA PECsed 21d	2.219	0.405	0.129	0.287	0.106	0.369

Myclobutanil at FOCUS Step 3 – 1 x 48 g as/ha

Concentration	PEC Values					
	D6 d (3.5 m)	R1 p (6 m)	R1 s (4 m)	R2 s (4 m)	R3 s (4 m)	R4 s (4 m)
(µg/L)						
Max. PECsw	0.824	0.031	0.602	0.806	0.842	0.592
TWA PECsw 21d	0.291	0.028	0.023	0.012	0.011	0.020

(µg/kg dry weight)						
Max. PECsed	1.334	0.180	0.269	0.213	0.145	0.269
TWA PECsed 21d	1.074	0.180	0.112	0.128	0.047	0.108

Accumulation myclobutanil PEC sediment values to encompass the concentrations from all FOCUS scenarios

	Predicted maximum plateau concentration in sediment in µg a.s./kg soil (on the basis of DT_{50}(sediment) of 626 days)
Vines (D6 ditch, default step 3 buffer distance, 3.5m)	8.77

Summary of PEC_{SW} and PEC_{SED} values for "butyric (Step 2) following use of Systhane 20EW on vines (late application)

"Butyric acid" metabolite at FOCUS Step 2 – 4 x 48 g as/ha, Worst case given by S Europe, Mar-May application

Time (days)	South Europe, Mar-May			
	PECsw (µg/L)		PECsed (µg/kg)	
	Actual	TWA	Actual	TWA
0	0.38	-	0.05	-
1	0.38	0.38	0.05	0.05
2	0.38	0.38	0.05	0.05
4	0.38	0.38	0.05	0.05
7	0.38	0.38	0.05	0.05
14	0.37	0.38	0.05	0.05
21	0.37	0.37	0.05	0.05
28	0.37	0.37	0.05	0.05
42	0.37	0.37	0.05	0.05
50	0.36	0.37	0.05	0.05
100	0.35	0.36	0.05	0.05

PEC (ground water) (Annex IIIA, point 9.2.1)

Method of calculation and type of study (*e.g.* modelling, monitoring, lysimeter)	Modelling using FOCUS models, with appropriate FOCUS gw scenarios, according to FOCUS guidance. Model(s) used: FOCUSPEARL 3.3.3 and FOCUSPELMO 3.3.2 Scenarios: Chateaudun, Hamburg, Kremsmünster, Piacenza, Porto, Sevilla, Thiva Crop: vines Myclobutanil: Tier 1 – geometric mean SFO DT_{50lab} 305 d (normalised to pF2/20°C (Q_{10} 2.58)). Higher tier – geometric mean SFO $DT_{50field}$ 228 d (day-lengths normalised to 20°C (Q_{10} 2.58). K_{foc}: mean 517, $^1/_n$= 0.88. Molecular weight : 288.8 Vapour pressure: 1.98 10^{-4} Pa Water solubility : 132 mg/L Metabolite myclobutanil butyric acid: Geometric mean DT_{50lab} 16.2 d (normalised to pF2/20°C (Q_{10} 2.58)). K_{foc}: mean 13.2 mL/g, $^1/_n$= 0.95 Molecular weight : 290.8 Vapour pressure: 1.98 10^{-4} Pa (as surrogate from a.s.) Water solubility: 132 mg/L (as surrogate from a.s.) Formation fraction: 0.6
Application rate	Application rate: 48 g/ha. (a) No. of applications: 4 (supported GAP) Time of application): 15 May to 14 Jun, 10 d intervals (b) No. of applications: 3 Time of application): 25 May to 14 Jun, 10 d intervals

$PEC_{(gw)}$ Maximum concentration	-
Average annual concentration (Results quoted for modelling with FOCUS gw scenarios, according to FOCUS guidance.)	FOCUSPEARL annual average concentrations (80th percentile) according to FOCUS guidance: "Tier 1" using geomean standardised (temperature and moisture) DT_{50} lab myclobutanil: <0.001-0.479 µg/L (PIA) from 4 x 48 g as/ha <0.001-0.295 µg/L (PIA) from 3 x 48 g as/ha Butyric acid metabolite: 0.143-0.872 µg/L (HAM) from 4 x 48 g as/ha 0.096-0.589 µg/L (HAM) from 3 x 48 g as/ha "Higher tier" using geomean standardised (temperature only) DT_{50} field for parent

myclobutanil:
<0.001-0.211 µg/L (PIA) from 4 x 48 g as/ha
<0.001-0.125 µg/L (PIA) from 3 x 48 g as/ha
Butyric acid metabolite:
0.132-0.810 µg/L (HAM) from 4 x 48 g as/ha
0.089-0.551 µg/L (HAM) from 3 x 48 g as/ha

FOCUSPELMO annual average concentrations (80th percentile) according to FOCUS guidance:

"Tier I" using geomean standardised (temperature and moisture) DT_{50} lab
myclobutanil:
<0.001-0.354 µg/L (PIA) from 4 x 48 g as/ha
<0.001-0.216 µg/L (PIA) from 3 x 48 g as/ha
Butyric acid metabolite:
0.153-0.850 µg/L (HAM) from 4 x 48 g as/ha
0.105-0.573 µg/L (HAM) from 3 x 48 g as/ha

"Higher tier" using geomean standardised (temperature only) DT_{50} field for parent
myclobutanil:
<0.001-0.127 µg/L (PIA) from 4 x 48 g as/ha
<0.001-0.073 µg/L (PIA) from 3 x 48 g as/ha
Butyric acid metabolite:
0.137-0.816 µg/L (HAM) from 4 x 48 g as/ha
0.094-0.557 µg/L (HAM) from 3 x 48 g as/ha

(see detailed results in tables below)

Tier I PECgw (lab DT_{50} for parent and metabolite)

Scenario	80th 'ile Annual Average PECgw (µg/L)								
	CHA	HAM	JOK	KRE	OKE	PIA	POR	SEV	THI
Worst case GAP - FOCUSPEARL									
Myclobutanil	0.217	0.133	-	0.105	-	0.479	<0.001	0.071	0.173
"Butyric Acid"	0.606	0.872	-	0.493	-	0.633	0.143	0.293	0.307
Worst case GAP - FOCUSPELMO									
Myclobutanil	0.163	0.042	-	0.060	-	0.354	<0.001	<0.001	0.061
"Butyric Acid"	0.510	0.850	-	0.520	-	0.613	0.202	0.153	0.264
Realistic case GAP - FOCUSPEARL									
Myclobutanil	0.124	0.075	-	0.056	-	0.295	<0.001	0.040	0.100
"Butyric Acid"	0.405	0.589	-	0.330	-	0.435	0.096	0.195	0.204
Realistic case GAP - FOCUSPELMO									
Myclobutanil	0.093	0.019	-	0.029	-	0.216	<0.001	<0.001	0.032
"Butyric Acid"	0.341	0.573	-	0.348	-	0.420	0.136	0.105	0.176

- FOCUS scenario not relevant for vines

Higher Tier PECgw (field DT_{50} for parent and lab DT_{50} for metabolite)

Scenario	80th 'ile Annual Average PECgw (µg/L)								
	CHA	HAM	JOK	KRE	OKE	PIA	POR	SEV	THI
Worst case GAP - FOCUSPEARL									
Myclobutanil	0.060	0.033	-	0.026	-	0.211	<0.001	0.013	0.046
"Butyric Acid"	0.539	0.810	-	0.456	-	0.607	0.132	0.236	0.257
Worst case GAP - FOCUSPELMO									
Myclobutanil	0.036	0.006	-	0.009	-	0.127	<0.001	<0.001	0.008
"Butyric Acid"	0.467	0.816	-	0.484	-	0.571	0.187	0.137	0.223
Realistic case GAP - FOCUSPEARL									
Myclobutanil	0.032	0.018	-	0.012	-	0.125	<0.001	0.007	0.025
"Butyric Acid"	0.361	0.551	-	0.306	-	0.416	0.089	0.156	0.171
Realistic case GAP - FOCUSPELMO									
Myclobutanil	0.019	0.003	-	0.004	-	0.073	<0.001	<0.001	0.004
"Butyric Acid"	0.313	0.557	-	0.324	-	0.392	0.126	0.094	0.149

- FOCUS scenario not relevant for vines

Fate and behaviour in air (Annex IIA, point 7.2.2, Annex III, point 9.3)

Direct photolysis in air ‡	Not required
Quantum yield of direct phototransformation	Not required
Photochemical oxidative degradation in air ‡	DT_{50} : 7.6 hours, assuming global OH-concentration of 1.5×10^6 OH radicals/cm^3 and 12 hour day
Volatilization ‡	from plant surfaces: not significant (up to *ca* 2.6% AR) under the conditions of a wind tunnel study (24 hours in an air-flow at *ca* 1 m/s).
	from soil: minimal under the conditions of a wind tunnel study (24 hours in an air-flow at 1-1.5 m/s). (2 studies)

PEC (air)

Method of calculation	Not required

$PEC_{(a)}$

Maximum concentration	Not required

Definition of the Residue (Annex IIA, point 7.3)

Environmental occurring residues requiring further assessment by other disciplines (toxicology and ecotoxicology) and or requiring consideration for groundwater exposure.	Residue definition for risk assessment Soil: myclobutanil Surface Water : myclobutanil, myclobutanil butyric acid Sediment: myclobutanil, myclobutanil butyric acid

	Ground water: myclobutanil, myclobutanil butyric acid. Note: since the "butyric acid" metabolite PECgw was >0.1 µg/L, its relevance to groundwater has been assessed (not relevant) Air : myclobutanil Residue definition for monitoring Soil : myclobutanil isomers Water : myclobutanil isomers Air : myclobutanil isomers

Monitoring data, if available (Annex IIA, point 7.4)

Soil (indicate location and type of study)	Not available
Surface water (indicate location and type of study) Ground water (indicate location and type of study)	The notifier submits a summary of the monitoring data available in European countries. Myclobutanil is not widely monitored in surface water and groundwater across Europe (15 EU Member States, plus Norway and Switzerland). The data provide a limited assessment of the situation.
Air (indicate location and type of study)	Not available

Classification and proposed labelling (Annex IIA, point 10)

with regard to fate and behaviour data	Candidate for R53

Revised in February 2010
Revised in May 2010
Revised in May 2010 by EFSA

Ecotoxicology

Effects on terrestrial vertebrates (Annex IIA, point 8.1, Annex IIIA, points 10.1 and 10.3)

Species	Test substance	Time scale	End point (mg/kg bw/day)	End point (mg/kg feed)
Birds ‡				
Colinus virginianus	myclobutanil	acute	**LD_{50} = 510**	-
Colinus virginianus	myclobutanil	short-term	**LC_{50} > 567**	> 5000
Anas platyrhynchos	myclobutanil	short-term	LC_{50} > 1544	> 5000
Anas platyrhynchos	myclobutanil	long-term	NOEC = 31.6	260
Colinus virginianus	myclobutanil	long-term	**NOEC = 24.2**	260
Mammals ‡				
Male rat	myclobutanil	acute	**LD_{50} = 1600**	-
Rat	myclobutanil	long-term	**NOEL = 16**	-
Additional higher tier studies ‡				
Not required.				

Toxicity/exposure ratios for terrestrial vertebrates (Annex IIIA, points 10.1 and 10.3)

Crop and application rate : grapes, 4 x 0.048 kg a.s./ha

Indicator species/Category[2]	Time scale	ETE	TER[1]	Annex VI Trigger[3]
Tier 1 (Birds)				
Insectivorous bird	acute	2.60	197	10
Insectivorous bird	short-term	1.45	> 392	10
Insectivorous bird	long-term	1.45	16.7	5
Earthworm-eating bird	long-term	0.149	162	5
Fish-eating bird	long-term	0.001	26496	5
Higher tier refinement (Birds)				
Not required.				
Tier 1 (Mammals)				
Small herbivorous mammal	acute	9.07	176	10
Small herbivorous mammal	long-term	3.09	5.18	5
Earthworm-eating mammal	long-term	0.190	84	5
Fish-eating mammal	long-term	0.0006	28299	5
Higher tier refinement (Mammals)				
Small herbivorous mammal	Long-term	1.53	10.4 (residues)	5

[1] in higher tier refinement provide brief details of any refinements used (e.g., residues, PT, PD or AV)

[2] for cereals indicate if it is early or late crop stage
[3] If the Annex VI Trigger value has been adjusted during the risk assessment of the active substance (e.g. many single species data), it should appear in this column.

Endocrine disruption

Statement of the notifier:
"Possible endocrine effects are taken into consideration by the two reproduction studies in birds in setting a NOEC which is used in demonstrating an acceptable risk assessment for birds. Furthermore, regarding the results of both studies, the RMS concluded in the DAR "The test material did not adversely affect any parameters of reproduction." Therefore, the endocrine issue for birds is addressed."

Conclusion of the RMS:
RMS agrees with the statement of the notifier.
In the section on mammalian toxicology, no specific concern with regard to endocrine disruption in mammals was identified.
RMS has made a public literature search and there was no indication of potential endocrine disrupting effects of myclobutanil in birds.
Based on the risk assessment conducted for insectivorous, vermivorous and piscivorous birds, the acute, short-term and long-term risk of myclobutanil to birds is low.
Therefore, RMS is of the opinion that the risk for endocrine disrupting effects in birds is low.

Toxicity data for aquatic species (most sensitive species of each group) (Annex IIA, point 8.2, Annex IIIA, point 10.2)

Group	Test substance	Time-scale (Test type)	End point	Toxicity[1] (mg/L)
Laboratory tests ‡				
Fish				
Oncorhynchus mykiss	myclobutanil	96 h (static)	Mortality, LC_{50}	**2.0 mg a.s./L** (initial)
Lepomis macrochirus	myclobutanil	96 h (static)	Mortality, LC_{50}	4.1 mg a.s./L (mm)
Cyprinodon variegatus	myclobutanil	96 h (flow-through)	Mortality, LC_{50}	4.7 mg a.s./L (mm)
Oncorhynchus mykiss	myclobutanil	21 d (flow-through)	Growth NOEC	**0.2 mg a.s./L** (nom)
Pimephales promelas	myclobutanil	35 d (flow-through)	Growth NOEC	0.98 mg a.s./L (mm)
Oncorhynchus mykiss	Systhane 20 EW	96 h (static)	Mortality, LC_{50}	10.3 mg form/L (**2.04 mg a.s./L**) (mm)
Oncorhynchus mykiss	myclobutanil butyric acid	96 h (static)	Mortality, LC_{50}	> 100 mg/L (nom)
Aquatic invertebrate				
Daphnia magna	myclobutanil	48 h (static)	Mortality, EC_{50}	17 mg a.s./L (mm)
Mysidopsis bahia	myclobutanil	96 h (flow-through)	Mortality, EC_{50}	**0.24 mg a.s./L** (mm)
Crassostrea virginica	myclobutanil	96 h (flow-through)	Mortality, EC_{50}	0.72 mg a.s./L (mm)

Group	Test substance	Time-scale (Test type)	End point	Toxicity[1] (mg/L)
Daphnia magna	myclobutanil	21 d (semi-static)	Reproduction, NOEC	**1.0 mg a.s./L** (nom)
Daphnia magna	Systhane 20 EW	48 h (static)	Mortality, EC_{50}	7.1 mg form/L (**1.41 mg a.s./L**) (mm)
Daphnia magna	GF-1317	21 d (semi-static)	Reproduction, NOEC	1.3 mg form/L (**0.27 mg a.s./L**) (nom)
Daphnia magna	myclobutanil butyric acid	48 h (static)	Mortality, EC_{50}	> 100 mg/L (nom)
Sediment dwelling organisms				
Chironomus riparius	myclobutanil	30 d (static) s/w system	NOEC	**4.98 mg a.s./L** (mm) **6.07 - 13.97 mg a.s./kg** (mm) recalculated sediment concentration on day 0 – day 30. For risk assessment purpose the lower concentration should be used.
Algae				
Desmodesmus subspicatus	myclobutanil	96 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	2.655 mg a.s./L 6.7 mg a.s./L (nom)
Pseudokirchneriella subcapitata	myclobutanil	120 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	**1.1 mg a.s./L** 1.2 mg a.s/L (mm)
Pseudokirchneriella subcapitata	Systhane 20 EW	96 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	8.6 mg form/L (1.70 mg a.s./L) > 5.0 mg form/L (> **0.99 mg a.s./L**) (mm)
Pseudokirchneriella subcapitata	myclobutanil butyric acid	96 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	56.2 mg/L (mm) 69.2 mg/L (mm)
Higher plant				
Lemna gibba	myclobutanil butyric acid	7 d (static)	Fronds, EC_{50}	> 105 mg/L (mm)
Microcosm or mesocosm tests				
Not required. A microcosm or mesocosm study is not required since TER_a > 100 and TER_{lt} > 10 with appropriate buffer zones between the sprayed area and water bodies.				

[1] indicate whether based on nominal ($_{nom}$) or mean measured concentrations ($_{mm}$). In the case of preparations indicate whether end points are presented as units of preparation or a.s.

Systhane 20 EW : formulation containing 19.8 % myclobutanil (batch n°: DK-2102-A)
GF-1317 : formulation containing 20.6 % myclobutanil (batch n°: E1743-16)

Toxicity/exposure ratios for the most sensitive aquatic organisms (Annex IIIA, point 10.2)

FOCUS Step 1

FOCUS Step 2

No acceptable aquatic risk assessment based on FOCUS step 1 and step 2 calculations for the parent myclobutanil.

The risk assessment for the metabolite myclobutanil butyric acid is based on FOCUS step 2 calculations.

Toxicity Exposure Ratio's (TER's) for aquatic organisms exposed to the metabolite myclobutanil butyric acid in surface water for use in vines (4 x 0.048 kg a.s./ha, late application) based on FOCUS step 2 calculations (worst case given by S Europe, Mar-May application)

Test substance	N/S	Organism	Toxicity end point (mg/L)	Time scale	PEC_{sw} (µg/L)	TER	Annex VI Trigger
myclobutanil butyric acid	S	*Oncorhynchus mykiss*	> 100	acute	0.38	263158	100
myclobutanil butyric acid	S	*Daphnia magna*	> 100	acute	0.38	263158	100
myclobutanil butyric acid	S	*Pseudokirchneriella subcapitata*	56.2	acute	0.38	147895	10
myclobutanil butyric acid	S	*Lemna gibba*	> 105	acute	0.38	276316	10

Refined aquatic risk assessment using higher tier FOCUS modelling.

FOCUS Step 3

Toxicity Exposure Ratio's (TER's) for aquatic organisms exposed to myclobutanil in surface water for use in vines (4 x 0.048 kg a.s./ha, late application) based on FOCUS step 3 calculations

Test substance	Scena-rio	Water body type	Test species	Time-scale	End-point (mg a.s./L)	Buffer-zone	Max PEC_{SW}, (µg a.s./L)	TER	Annex VI Trigger value
myclobutanil	D 6	ditch	*Oncorhynchus mykiss*	96 h	2.0	3.5 m	1.018	1965	100
	R 1	pond				6 m	0.074	27027	100
	R 1	stream				4 m	0.880	2273	100
	R 2	stream				4 m	0.666	3003	100
	R 3	stream				4 m	0.700	2857	100
	R 4	stream				4 m	1.956	1022	100
myclobutanil	D 6	ditch	*Oncorhynchus mykiss*	21 d	0.2	3.5 m	1.018	196	10
	R 1	pond				6 m	0.074	2703	10
	R 1	stream				4 m	0.880	227	10
	R 2	stream				4 m	0.666	300	10
	R 3	stream				4 m	0.700	286	10

	R 4	stream				4 m	1.956	102	10
myclobutanil	D 6	ditch	*Mysidopsis bahia*	96 h	0.24	3.5 m	1.018	236	100
	R 1	pond				6 m	0.074	3243	100
	R 1	stream				4 m	0.880	273	100
	R 2	stream				4 m	0.666	360	100
	R 3	stream				4 m	0.700	343	100
	R 4	stream				4 m	1.956	123	100
myclobutanil	D 6	ditch	*Daphnia magna*	21 d	1.0	3.5 m	1.018	982	10
	R 1	pond				6 m	0.074	13514	10
	R 1	stream				4 m	0.880	1136	10
	R 2	stream				4 m	0.666	1502	10
	R 3	stream				4 m	0.700	1429	10
	R 4	stream				4 m	1.956	511	10
myclobutanil	D 6	ditch	*Pseudokirchneriella subcapitata*	120 h	1.1	3.5 m	1.018	1081	10
	R 1	pond				6 m	0.074	14865	10
	R 1	stream				4 m	0.880	1250	10
	R 2	stream				4 m	0.666	1652	10
	R 3	stream				4 m	0.700	1571	10
	R 4	stream				4 m	1.956	562	10
myclobutanil	D 6	ditch	*Chironomus riparius*	30 d	4.98	3.5 m	1.018	4892	10
	R 1	pond				6 m	0.074	67297	10
	R 1	stream				4 m	0.880	5659	10
	R 2	stream				4 m	0.666	7477	10
	R 3	stream				4 m	0.700	7114	10
	R 4	stream				4 m	1.956	2546	10

Toxicity Exposure Ratio's (TER's) for aquatic organisms exposed to myclobutanil in sediment for use in vines (4 x 0.048 kg a.s./ha, late application) based on worst-case PEC_{SED} accumulation

Test substance	Scena-rio	Water body type	Test species	Time-scale	End-point (mg a.s./kg)	Buffer-zone	Max PEC_{SED}, (µg a.s./kg)	TER	Annex VI Trigger value
myclobutanil	D 6	ditch	*Chironomus riparius*	30 d	6.07	3.5 m	8.770	692	10

Toxicity Exposure Ratio's (TER's) for aquatic organisms exposed to formulations containing myclobutanil in surface water for use in vines (4 x 0.048 kg a.s./ha, late application) based on FOCUS step 3 calculations

Test substance	Scena-rio	Water body type	Test species	Time-scale	End-point (mg a.s./L)	Buffer-zone	Max PEC_{SW}, (µg a.s./L)	TER	Annex VI Trigger value
Systhane 20 EW	D 6	ditch	*Oncorhynchus mykiss*	96 h	2.04	3.5 m	1.018	2004	100
	R 1	pond				6 m	0.074	27568	100
	R 1	stream				4 m	0.880	2318	100
	R 2	stream				4 m	0.666	3063	100
	R 3	stream				4 m	0.700	2914	100
	R 4	stream				4 m	1.956	1043	100
Systhane 20 EW	D 6	ditch	*Daphnia magna*	48 h	1.41	3.5 m	1.018	1385	100
	R 1	pond				6 m	0.074	19054	100
	R 1	stream				4 m	0.880	1602	100
	R 2	stream				4 m	0.666	2117	100
	R 3	stream				4 m	0.700	2014	100
	R 4	stream				4 m	1.956	721	100
GF-1317	D 6	ditch	*Daphnia magna*	21 d	0.27	3.5 m	1.018	265	10
	R 1	pond				6 m	0.074	3649	10
	R 1	stream				4 m	0.880	307	10
	R 2	stream				4 m	0.666	405	10
	R 3	stream				4 m	0.700	386	10
	R 4	stream				4 m	1.956	138	10
Systhane 20 EW	D 6	ditch	*Pseudokirchneriella subcapitata*	96 h	0.99	3.5 m	1.018	972	10
	R 1	pond				6 m	0.074	13378	10
	R 1	stream				4 m	0.880	1125	10
	R 2	stream				4 m	0.666	1486	10
	R 3	stream				4 m	0.700	1414	10
	R 4	stream				4 m	1.956	506	10

Systhane 20 EW : formulation containing 19.8 % myclobutanil (batch n°: DK-2102-A)
GF-1317 : formulation containing 20.6 % myclobutanil (batch n°: E1743-16)

According to the German approach the potential for **endocrine disruption in fish** can be addressed based on the early life stage study with *Pimephales promelas*. The endpoint NOEC (35 d) = 0.98 mg a.s./L is divided by a safety factor of 5 (as for other triazoles), which results in $NOEC_{corrected}$ = 0.196 mg a.s./L.

Chronic Toxicity Exposure Ratio's (TER's) for fish exposed to myclobutanil in surface water for use in vines (4 x 0.048 kg a.s./ha, late application) based on FOCUS step 3 calculations

Test substance	**Scena-rio**	**Water body type**	**Test species**	**Time-scale**	**End-point (mg a.s./L)**	**Buffer-zone**	**Max PEC_{SW}, (µg a.s./L)**	**TER**	**Annex VI Trigger value**
myclobutanil	D 6	ditch	*Pimephales promelas*	35 d	0.196	3.5 m	1.018	193	10
	R 1	pond				6 m	0.074	2649	10
	R 1	stream				4 m	0.880	223	10
	R 2	stream				4 m	0.666	294	10
	R 3	stream				4 m	0.700	280	10
	R 4	stream				4 m	1.956	100	10

During the expert consultation (PRAPeR TC 30) it was remarked that a lower chronic endpoint for fish is available.
According to the German approach the potential for endocrine disruption in fish can be addressed based on the fish juvenile growth study with *Oncorhynchus mykiss*. The endpoint NOEC (21 d) > 0.2 mg a.s./L is divided by a safety factor of 5 (as for other triazoles), which results in $NOEC_{corrected}$ = 0.04 mg a.s./L.

Chronic Toxicity Exposure Ratio's (TER's) for fish exposed to myclobutanil in surface water for use in vines (4 x 0.048 kg a.s./ha, late application) based on FOCUS step 3 calculations

Test substance	Scena-rio	Water body type	Test species	Time-scale	End-point (mg a.s./L)	Buffer-zone	Max PEC_{SW}, (µg a.s./L)	TER	Annex VI Trigger value
myclobutanil	D 6	ditch	*Oncorhynchus mykiss*	21 d	0.04	3.5 m	1.018	39	10
	R 1	pond				6 m	0.074	541	10
	R 1	stream				4 m	0.880	45	10
	R 2	stream				4 m	0.666	60	10
	R 3	stream				4 m	0.700	57	10
	R 4	stream				4 m	1.956	20	10

The chronic TER values based on the relevant endpoints to assess potential for endocrine disruption are acceptable. The calculations based on the endpoint for *Oncorhynchus mykiss* are cleary a worst-case assumption. Hence, the risk for endocrine disrupting effects in fish is low.

FOCUS Step 4

Acceptable risk of myclobutanil and the formulations Systhane 20 EW and GF-1317 based on FOCUS step 3 scenarios.

Acceptable risk of the metabolite myclobutanil butyric acid based on FOCUS step 2 scenarios.

Bioconcentration				
	Active substance	Myclobutanil butyric acid	Meta-bolite2	Meta-bolite3
$logP_{O/W}$	2.89 – 3.5	1.29**		
Bioconcentration factor (BCF)[1] ‡	Since the log P_{OW} of myclobutanil is around 3, the MS agreed during Peer Review that a bioaccumulation study in fish is required. BCF in whole fish = 8.3			
Annex VI Trigger for the bioconcentration factor	100	-	-	-
Clearance time (days) (CT_{50})	0.8 days	-	-	-
(CT_{90})	1.8 days	-	-	-
Level and nature of residues (%) in organisms after the 14 day depuration phase	Radioactive residues eliminated by Day 3 of depuration phase. Monohydroxylated metabolites comprising ~35% of TRR were reported..	-	-	-

[1] only required if log $P_{O/W}$ >3.
* based on total ^{14}C or on specific compounds
** based on QSAR estimated by KOWWIN module of EPI Suite v.4.0

Effects on honeybees (Annex IIA, point 8.3.1, Annex IIIA, point 10.4)

Test substance	Acute oral toxicity (LD_{50} µg/bee)	Acute contact toxicity (LD_{50} µg/bee)
Systhane 20 EW[1]	> **171 µg form/bee** (33.9 µg a.s./bee)	> **200 µg form/bee** (39.6 µg a.s./bee)
Field or semi-field tests		
Not required. The hazard quotients for oral and contact toxicity are below 50, so no higher tier testing is necessary.		

[1] for preparations indicate whether end point is expressed in units of a.s. or preparation

Systhane 20 EW : formulation containing 19.8 % myclobutanil (batch n°: DK-2102-A)

Hazard quotients for honey bees (Annex IIIA, point 10.4)

Crop and application rate : grapes, 4 x 0.048 kg a.s./ha

Test substance	Route	Hazard quotient	Annex VI Trigger
Systhane 20 EW	oral	< 1.4	50
	contact	< 1.2	50

Effects on other arthropod species (Annex IIA, point 8.3.2, Annex IIIA, point 10.5)

Laboratory tests with standard sensitive species
No such tests were performed.

Further laboratory and extended laboratory studies ‡

Species	Life stage	Test substance, substrate and duration	Dose (g a.s./ha)[1,2]	End point	effect[3]	Trigger value
Laboratory tests						
Typhlodromus pyri	proto-nymphs	Systhane 20 EW, glass plates, 14 d	36 g a.s./ha, initial	Corrected mortality Reproduction	50.5 % - 67.3 %	50 % 50 %
Coccinella septempunctata	larvae	Systhane 20 EW, glass plates, 2 + 5 weeks	36 g a.s./ha, initial	Corrected mortality Reproduction	11.9 % -51.8 %	50 % 50 %
Pardosa sp.	-	Systhane 20 EW, sand, 14 d	45 g a.s./ha, initial	Corrected mortality Food consumption	5.6 % - 33.3 %	50 % 50 %
Extended laboratory tests						
Aphidius rhopalosiphi	adult females	Systhane 20 EW, barley plants, 2 + 12 d	36 g a.s./ha, initial	Corrected mortality Reproduction	0.00 % - 43.0 %	50 % 50 %
Aphidius rhopalosiphi	adult females	Systhane 20 EW, barley plants, 2 d + 10 d	90 g a.s./ha, initial	Corrected mortality Reproduction	41.4 % - 52.8 %	50 % 50 %
Aged residue tests						
Aphidius rhopalosiphi	adult females	Systhane 20 EW, barley plants, 2 d + 11 d	288 g a.s./ha, 0DAA	Corrected mortality Reproduction	0.00 % + 10.3 %	50 % 50 %
			780 g a.s./ha, 0DAA	Corrected mortality Reproduction	0.00 % – 10.6 %	50 % 50 %
			1200 g a.s./ha, 0DAA	Corrected mortality Reproduction	6.67 % + 2.2 %	50 % 50 %
Chrysoperla carnea	larvae	Systhane 20 EW, bean leaves	307 g a.s./ha, 0DAA	Corrected mortality Reproduction	11.43 % + 18.7 %	50 % 50 %
			766 g a.s./ha, 0DAA	Corrected mortality Reproduction	28.57 % + 26.3 %	50 % 50 %
			1380 g a.s./ha, 0DAA	Corrected mortality Reproduction	40.0 % + 3.9 %	50 % 50 %

[1] indicate whether initial or aged residues
[2] for preparations indicate whether dose is expressed in units of a.s. or preparation
[3] indicate if positive percentages relate to adverse effects or not

(for Reproduction parameter : negative % = adverse effect; positive % = no adverse effect)

Systhane 20 EW : formulation containing 19.8 % myclobutanil (batch n°: DK-2102-A)
formulation containing 211 g/L myclobutanil (batch n°: QC2388R301)

Corrected mortality : positive values : adverse effects
Food consumption : negative values : adverse effects; positive values : no adverse effects
Reproduction : negative values : adverse effects; positive values : no adverse effects

Field or semi-field tests
In the semi-field test with *Aphidius rhopalosiphi*, hop plants were sprayed at 54 g a.s./ha and at 300 g a.s./ha, both applied 4 times at 10 ± 2 days interval. Untreated barley plants, infested with aphids were placed next to the treated hop plants. The first bioassay was performed after the 1st treatment and the second bioassay was performed after the 4th treatment. The reduction in reproductive ability at the application rate of 54 g a.s./ha was 36 % (bioassay 1) and – 1.6 % (bioassay 2). The reduction in reproductive ability at the application rate of 300 g a.s./ha was 1 % (bioassay 1) and 16.7 % (bioassay 2). Systhane 20 EW has no effects on *Aphidius rhopalosiphi* up to 4 x 300 g a.s./ha. In the field test with *Typhlodromus pyri*, an apple orchard in southern Germany was treated with 0.45 L Systhane 20 EW/ha (89 mL a.s./ha) and with 0.9 L Systhane 20 EW/ha (178 mL a.s./ha), both applied 9 times between the beginning of June and the beginning of September. No effects were observed for the predatory mites (eggs and adults) and for the spider mites (eggs and adults) up to 9 x 0.9 L Systhane 20 EW/ha (equivalent to 9 x 180 g a.s./ha).

Effects on earthworms, other soil macro-organisms and soil micro-organisms (Annex IIA points 8.4 and 8.5. Annex IIIA, points, 10.6 and 10.7)

Test organism	Test substance	Time scale	End point[1]
Earthworms			
Lumbricus terrestris	myclobutanil ‡	acute	LC_{50} = 250 mg a.s./kg soil d.w. $LC_{50\ corr}$ = **125 mg a.s./kg soil d.w.**
Eisenia fetida	Systhane 24 E	acute	LC_{50} = 384 mg form/kg soil d.w. (99 mg a.s./kg soil d.w.) $LC_{50\ corr}$ = **49.5 mg a.s./kg soil d.w.**
Eisenia fetida	Systhane 20 EW	long-term	NOEC = 10.3 mg a.s./kg soil d.w. $NOEC_{corr}$ = **5.15 mg a.s./kg soil d.w.**
Eisenia fetida	myclobutanil butyric acid	acute	LC_{50} > 1000 mg/kg soil d.w. $LC_{50\ corr}$ > 500 mg/kg soil d.w.
Other soil macro-organisms			
Not required.			
Collembola			
Folsomia candida	Systhane 20 EW	long-term	NOEC = 100 mg form/kg soil d.w. (20.5 mg a.s./kg soil d.w.) $NOEC_{corr}$ = **10.25 mg a.s./kg soil d.w.**
Soil micro-organisms			
Nitrogen mineralisation	Systhane 24 E	28 d	- 3 % effect at day 28 at 2.93 mg form/kg soil d.w. (0.76 mg a.s./kg soil d.w.)
Carbon mineralisation	Systhane 24 E	28 d	- 4 % effect at day 28 at 2.93 mg form/kg soil d.w. (0.76 mg a.s./kg soil d.w.)
Field studies[2]			
An earthworm bioconcentration study with myclobutanil (Hoberg J.R., 1993) was conducted. Earthworms were exposed for 14 days to soil treated with myclobutanil. The bioconcentration factor was 0.46 – 0.47 with an uptake rate constant k_u of 1.19 $days^{-1}$ and a depuration rate constant k_d of 2.52 $days^{-1}$. These results demonstrated that the ^{14}C-myclobutanil does not readily bioconcentrate in tissue of *Eisenia fetida* over a 14-day period. The small amount of ^{14}C-residues that accumulated during the exposure were completely eliminated three days after transfer to untreated artificial soil. A litter bag test (Mallet M. J., 2004) was conducted on the edge of a field sown with winter barley. Treatment with a first application of 226 g a.s./ha and a second application of 117 g a.s./ha. A good earthworm population existed at the trial site. Myclobutanil had no adverse effect on the rate of breakdown of straw litter in soil at mean concentrations of 0.1247 – 0.1460 mg a.s./kg soil. This concentration covers the ~~worst case~~ PEC_{soil} of 0.090 mg a.s./kg soil ($PEC_{initial}$ after last application at 20 cm soil depth in grapes ~~apples~~).			

[1] indicate where end point has been corrected due to log Pow >2.0 (e.g. LC_{50corr})
[2] litter bag, field arthropod studies not included at 8.3.2/10.5 above, and earthworm field studies
Systhane 24 E : formulation containing 25.8 % myclobutanil (batch n° : DK-2195-A)
Systhane 20 EW : formulation containing 19.9 % myclobutanil (batch n° : ES-96018)

Toxicity/exposure ratios for soil organisms

Crop and application rate : grapes, 4 x 0.048 kg a.s./ha

Test organism	Test substance	Time scale	Soil PEC[2] (mg a.s./kg soil)	TER	Trigger
Earthworms					
Lumbricus terrestris	myclobutanil ‡	acute	PEC_{max} = 0.428 mg a.s./kg soil d.w.	292	10
Eisenia fetida	Systhane 24 E	acute	PEC_{max} = 0.428 mg a.s./kg soil d.w.	115	10
Eisenia fetida	Systhane 20 EW	long-term	PEC_{max} = 0.428 mg a.s./kg soil d.w.	12	5
Other soil macro-organisms					
Folsomia candida	Systhane 20 EW	long-term	PEC_{max} = 0.428 mg a.s./kg soil d.w.	23.9	5

[1] to be completed where first Tier triggers are breached
[2] indicate which PEC soil was used (e.g. plateau PEC)

Systhane 24 E : formulation containing 25.8 % myclobutanil (batch n° : DK-2195-A)
Systhane 20 EW : formulation containing 19.9 % myclobutanil (batch n° : ES-96018)

Effects on non target plants (Annex IIA, point 8.6, Annex IIIA, point 10.8)

In the vegatative vigour test, no test species exhibited morphological abnormalities, except for cabbage. In addition, > 25 % shoot inhibition was noted in onion shoot weight at 300 g a.s./ha, perennial ryegrass shoot weight at 900 g a.s./ha, cabbage shoot weight at 900 g a.s./ha, cucumber shoot weight at 300 and 900 g a.s./ha and soybean shoot length and shoot weight at 900 g a.s./ha.

In the seedling emergence test, shoot weight, but not shoot length or emergence, was affected at greater than 25 % inhibition in perennial ryegrass at the maximum application rate (300 g a.s./ha) and three times the maximum application rate (900 g a.s./ha). No other adverse effects at greater than 25 % inhibition were observed for any of the nine other test species.

Effects on biological methods for sewage treatment (Annex IIA 8.7)

Test type/organism	End point
Activated sludge	EC_{50} (myclobutanil, 3 h) = 71 mg a.s./L
Pseudomonas sp	-

Ecotoxicologically relevant compounds (consider parent and all relevant metabolites requiring further assessment from the fate section)

Compartment	
soil	myclobutanil
water	myclobutanil
sediment	myclobutanil
groundwater	myclobutanil

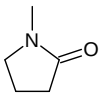
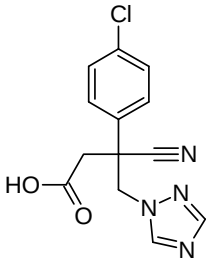
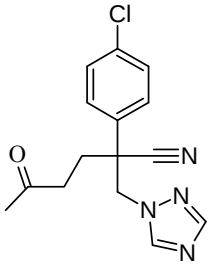
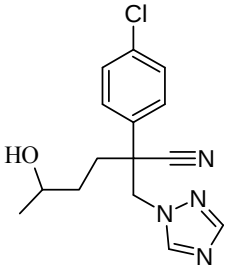
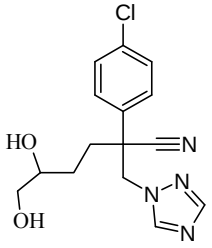
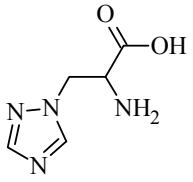
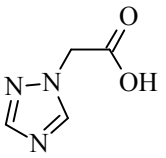
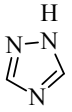
Classification and proposed labelling with regard to ecotoxicological data (Annex IIA, point 10 and Annex IIIA, point 12.3)

	RMS/peer review proposal
Active substance	N, R50

	RMS/peer review proposal
Preparation	N, R51 for Systhane 20 EW

The list of end points is available in a separate document.

APPENDIX B – USED COMPOUND CODE(S)

Code/Trivial name*	Chemical name**	Structural formula**
1-methylpyrrolidin-2-one	1-methylpyrrolidin-2-one	
myclobutanil butyric acid	(3*RS*)-3-(4-chlorophenyl)-3-cyano-4-(1*H*-1,2,4-triazol-1-yl)butanoic acid	
RH-9089	(2*RS*)-2-(4-chlorophenyl)-5-oxo-2-(1*H*-1,2,4-triazol-1-ylmethyl)hexanenitrile	
RH-9090	(2*RS*,5*RS*)-2-(4-chlorophenyl)-5-hydroxy-2-(1*H*-1,2,4-triazol-1-ylmethyl)hexanenitrile	
RH-0294	(2*RS*,5*RS*)-2-(4-chlorophenyl)-5,6-dihydroxy-2-(1*H*-1,2,4-triazol-1-ylmethyl)hexanenitrile	
triazolyl alanine	(2*RS*)-2-amino-3-(1*H*-1,2,4-triazol-1-yl)propanoic acid	
triazolyl acetic acid	1*H*-1,2,4-triazol-1-ylacetic acid	
1,2,4-triazole	1*H*-1,2,4-triazole	

* The metabolite name in bold is the name used in the conclusion

** ACD/ChemSketch, Advanced Chemistry Development, Inc., ACD/Labs Release: 12.00 Product version: 12.00 (Build 29305, 25 Nov 2008).

ABBREVIATIONS

ADI	acceptable daily intake
AOEL	acceptable operator exposure level
ARfD	acute reference dose
a.s.	active substance
bw	body weight
CA	Chemical Abstract
CAS	Chemical Abstract Service
CIPAC	Collaborative International Pesticide Analytical Council Limited
d	day
DAR	draft assessment report
DM	dry matter
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
ε	decadic molar extinction coefficient
EC_{50}	effective concentration
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINKS	European List of New Chemical Substances
EMDI	estimated maximum daily intake
ER50	emergence rate, median
EU	European Union
FAO	Food and Agriculture Organisation of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	good agricultural practice
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GS	growth stage
h	hour(s)
ha	hectare
hL	hectolitre
HPLC	high pressure liquid chromatography or high performance liquid chromatography
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
K_{oc}	organic carbon adsorption coefficient
L	litre
LC	liquid chromatography
LC-MS	liquid chromatography-mass spectrometry
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LC_{50}	lethal concentration, median
LD_{50}	lethal dose, median; dosis letalis media
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification (determination)
µg	microgram
mN	milli-Newton
MRL	maximum residue limit or level
MS	mass spectrometry
NESTI	national estimated short-term intake
NIR	near-infrared-(spectroscopy)
nm	nanometer
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
OC	organic carbon content
PEC	predicted environmental concentration
PEC_A	predicted environmental concentration in air
PEC_{soil}	predicted environmental concentration in soil
PEC_{SW}	predicted environmental concentration in surface water

PEC_{GW}	predicted environmental concentration in ground water
PHI	pre-harvest interval
pK_a	negative logarithm (to the base 10) of the dissociation constant
PPE	personal protective equipment
ppm	parts per million (10^{-6})
ppp	plant protection product
r^2	coefficient of determination
RPE	respiratory protective equipment
STMR	supervised trials median residue
TER	toxicity exposure ratio
TMDI	theoretical maximum daily intake
UV	ultraviolet
WHO	World Health Organisation
WG	water dispersible granule
yr	year