Conclusion regarding the peer review of the pesticide risk assessment of the active substance

metconazole

finalised: 13 January 2006

SUMMARY

Metconazole is one of the 52 substances of the second stage of the review programme covered by Commission Regulation (EC) No 451/2000[1], as amended by Commission Regulation (EC) No 1490/2002[2]. 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 metconazole in accordance with the provisions of Article 8(1) of the amended Regulation (EC) No 451/2000, which was received by the EFSA on 27 January 2004. Following a quality check on the DAR, the peer review was initiated on 16 April 2004 by dispatching the DAR for consultation of the Member States and the sole applicant BASF. Subsequently, the comments received on the DAR were examined by the rapporteur Member State and the need for additional data was agreed in an evaluation meeting in 27 September 2004. 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 April - Mai 2005.

A final discussion of the outcome of the consultation of experts took place with representatives from the Member States on 28 November 2005 leading to the conclusions as laid down in this report.

The conclusion was reached on the basis of the evaluation of the representative uses as fungicide as proposed by the applicant which comprises broadcast spraying to control foliar and ear diseases in cereals and oilseed rape at application rate up to 90 g metconazole per hectare. Metconazole can be used only as fungicide.
The representative formulated product for the evaluation was "Caramba 60 SL", a soluble concentrate (SL), registered in some EU Member States.

[1] OJ No L 53, 29.02.2000, p. 25
[2] OJ No L 224, 21.08.2002, p. 25

Adequate methods are available to monitor all compounds given in the respective residue definition. Residues in food and soil can be determined with a multi-method (the German S19 method has been validated). For the other matrices only single methods are available to determine residues of metconazole.
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.

The acute oral toxicity of metconazole is moderate (a classification Xn; R22 "Harmful if swallowed" is proposed). Metconazole is of low acute dermal and inhalatory toxicity. It is not a skin or eye irritant or a skin sensitiser. The relevant NOAEL for short term toxicity is 6.4 mg/kg bw/day. Adrenals, liver and spleen were detected as target organs. Overall, metconazole is not genotoxic. The NOAEL for chronic toxicity and carcinogenicity is 4.4 mg/kg bw/day. It was considered that the compound was unlikely to be classified as a carcinogenic substance. The NOAELs for parental, reproduction and offspring toxicity are 8 mg/kg bw/day; based on the absence of effect on fertility in the rat 2-generation study (only modification of fertility parameters at maternotoxic doses). Both compounds are embryo- and foetotoxic at doses also producing maternal toxicity in rat developmental toxicity studies. Therefore, classification as Repro Cat. 3 (Xn; R63) was agreed on. The Acceptable Daily Intake (ADI), the Acute Reference Dose (ARfD) and the Acceptable Operator Exposure Levels (AOEL) are 0.01 mg/kg bw/day based on an overall NOAEL of 4 mg/kg bw/d with a safety factor of 400 (the increased SF is due to teratogenic effects).
Operator exposure is below the AOEL when PPE is worn. The exposure during re-entry activities and for bystanders is negligible.

In the plant metabolism studies conducted in wheat and oilseed rape, metconazole, triazolyl alanine and triazolyl acetic acid were identified as the major components of the total residues in the edible plant parts of the tested crops. Triazolyl alanine is a common metabolite of triazole fungicides, and its toxicological profile was considered as sufficiently investigated. The residue of concern in cereals and oilseed crops is therefore metconazole only. The enrichment of edible plant parts of succeeding crops with metconazole was not sufficient to reach quantifiable levels, when metconazole is used according cGAP. A complete residue trials data base on wheat, rye, triticale and oilseed rape was provided for Northern and Southern Europe and allowed MRL proposals. For barley uses in Southern Europe additional trial data need to be submitted to confirm the compliance with currently proposed MRL based on Northern European trials. Due to low consumer exposure industrial or household processing studies are not required.
Since significant residues occur in potential feed stuff, metabolism studies have been submitted in lactating goats and laying hens. In lactating goats, metconazole undergoes an extensive metabolisation, but was still detected in edible goat matrices bar kidney. All the metabolites found in goat tissues have been recovered in the rat. In a non peer reviewed addendum (December 2005) RMS concluded that representative uses do not give rise to significant residues in animal products and MRLs do not need to be proposed. In contrast, estimates of possibly occurring residues levels in

animal matrices done by EFSA indicated that relevant residue levels might be expected in ruminant liver. According to current guidelines a feeding study with ruminants would be required and MRLs for food of animal origin (i.e. ruminant liver) need to be proposed.
In laying hens, the metabolic profile was not further investigated and no such data is currently required since the intake by poultry is not significant with regard to the representative uses.
The dietary risk assessment performed for different consumer groups indicates that there are no chronic and acute concerns related to dietary exposure resulting from the representative uses.

Sufficient data were available to demonstrate that in soil metconazole exhibits medium to high persistence based on northern and southern European field studies where applications were made in May and June. Consequently the available laboratory studies did not identify any major (>10% of applied radioactivity (AR)) soil metabolites. Mineralization of the 3,5-triazole-^{14}C radiolabel accounted for 10.3% AR in dark aerobic laboratory soil studies after 91 days. The formation of unextracted residues in the soil organic carbon was the significant sink (accounting for 12-28% AR at 91-112 days). Metconazole exhibited low mobility in soil (based on evidence from laboratory soil batch adsorption studies) There was no evidence that adsorption changed with variation in soil pH.

In natural sediment water systems (dark laboratory studies) metconazole dissipated from the water relatively rapidly by partitioning to sediment. Once in the sediment degradation was slow with metconazole exhibiting high to very high persistence. The 3,5-triazole-^{14}C-label, did not mineralize to CO_2 at all. Formation of unextracted sediment radioactivity (11-19%AR at 100 days) and the formation of up to 6 resolved minor (≤9% AR) metabolites (5 identified) accounted for the slow loss of metconazole in these static experimental systems. It is a concern, that from the acceptable standard guideline studies required and provided, in terms of accounting for the route of breakdown and completing the material balance of metconazole, it is only possible to conclude that metconazole is persistent in the sediment of aquatic systems (there was no evidence that the metabolites formed were mineralised, the only sink identified was unextracted sediment radioactivity). Based on the available data, photolysis is not expected to be a significant process in the breakdown of metconazole in natural aquatic systems.

The environmental exposure assessments available are sufficient to complete the necessary EU level estimates of Predicted Environmental Concentrations (PEC) for the representative uses applied for, for annex 1 listing. Because of the persistence of metconazole in soil and aquatic sediment it was necessary for exposure assessments to take into account the potential accumulation of metconazole in these environmental matrices from potential use in consecutive years. Member States must also do this when assessing potential uses of metconazole at the national level. Member States also need to carry out aquatic exposure and risk assessments from the drainage and runoff routes of exposure to surface water as these routes of entry have not been considered in the EU level assessments available.

FOCUS groundwater modelling indicated a low potential for groundwater contamination in vulnerable situations over a wide range of geoclimatic conditions across the EU for the uses assessed

in this conclusion. (At all 9 FOCUS groundwater scenarios annual average leachate concentrations of metconazole leaving the top 1m soil layer were predicted to be below the parametric legal drinking water limit of 0.1µg/L).

The acute and short-term risk to birds and the acute risk to mammals are low from the representative uses. The first tier TER values indicated a high long-term risk for insectivorous and herbivorous birds (TER of 2.3 to 3.1) and a high long-term risk to herbivorous mammals. The EPCO experts' meeting identified the requirement for further information to justify the choice of the focal species and data on more species to refine the long term risk to insectivorous birds. The experts' meeting agreed to the refinement of long-term exposure based on residue data in cereals. The long-term risk to herbivorous birds was shown to be low for both representative uses. However, further refinement steps are necessary to address the risk to small herbivorous mammals for the representative use in cereals (TER of 2.9). The acute and the long term risk to mammals from the representative use in oilseed rape are considered to be low. The risk to birds and mammals from secondary poisoning from uptake of contaminated earthworms was discussed at the experts' meeting. It was agreed that the TER calculations should be based on the plateau PECsoil plus one application. The resulting TER values for birds and mammals of 10.5 and 5.3 are above the Annex VI trigger of 5 indicating a low risk from the representative uses.
The risk to birds and mammals from uptake of contaminated drinking water was calculated by EFSA according to Sanco/4145/2000 in an addendum. The first tier TER values indicated a high short-term and long term risk to birds and a high long-term risk to mammals. A refined risk assessment for the uptake of contaminated drinking water is required for the intended uses in cereals and oilseed rape.

The acute risk to aquatic organisms is low. The long-term risk to fish and daphnids is high and risk mitigation measures such as buffer zones up to 15 m are required.

The Annex VI trigger values were not met for NTA in a first tier testing. The higher tier tests showed that the risk to non-target arthropods is low.

A field litter bag study has been performed at an application rate equivalent to the supported GAP. No effects were observed in the study after 3 months and after 6 months of exposure. As some drawbacks have been identified in the study, the experts' meeting set a data requirement to submit a new litter bag study available to the applicant. The evaluation of this new study would allow completing the risk assessment.

The risk to bees, other non-target arthropods, earthworms, soil non-target micro-organisms and non-target plants is considered to be low for the representative uses.

Key words: metconazole peer review, risk assessment, pesticide, fungicide

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BACKGROUND

Commission Regulation (EC) No 451/2000 laying down the detailed rules for the implementation of the second and third stages of the work program referred to in Article 8(2) of Council Directive 91/414/EEC, as amended by Commission Regulation (EC) No 1490/2002, regulates for the European Food Safety Authority (EFSA) the procedure of evaluation of the draft assessment reports provided by the designated rapporteur Member State. Metconazole is one of the 52 substances of the second stage covered by the amended Regulation (EC) No 451/2000 designating Belgium as rapporteur Member State.

In accordance with the provisions of Article 8(1) of the amended Regulation (EC) No 451/2000, Belgium submitted the report of its initial evaluation of the dossier on metconazole, hereafter referred to as the draft assessment report, to the EFSA on 27 January 2004. 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 8(5) of the amended Regulation (EC) No 451/2000 the revised version of the draft assessment report was distributed for consultation on 16 April 2004 to the Member States and the sole applicant BASF 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 in an evaluation meeting on 27 September 2004 on data requirements to be addressed by the notifier as well as issues for further detailed discussion at expert level. A representative of the notifier attended this meeting.

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 experts' meetings organised on behalf of the EFSA by the EPCO-Team at the Federal Office for Consumer Protection and Food Safety (BVL) in Braunschweig in April – May 2005. The reports of these meetings have been made available to the Member States electronically.

A final discussion of the outcome of the consultation of experts took place with representatives from Member States on 28 November 2005 leading to the conclusions as laid down in this report.

During the peer review of the draft assessment report and the consultation of technical experts no critical issues were identified for consultation of the Scientific Panel on Plant Health, Plant Protection Products and their Residues (PPR).

In accordance with Article 8(7) of the amended Regulation (EC) No 451/2000, this conclusion summarises the results of the peer review on the active substance and the representative formulation

evaluated as finalised at the end of the examination period provided for by the same Article. A list of the relevant end points for the active substance as well as the formulation is provided in appendix 1.

The documentation developed during the peer review was compiled as a **peer review report** comprising of the documents summarising and addressing the comments received on the initial evaluation provided in the rapporteur Member State's draft assessment report:

- the comments received
- the resulting reporting table (rev. 1-1 of 11 October 2004)
- the consultation report

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 (rev. 1-2 of 1 December 2005)

Given the importance of the draft assessment report including its addendum (compiled version of January 2006 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.

By the time of the presentation of this conclusion to the EU-Commission, the rapporteur Member State has made available amended parts of the draft assessment report (Volume 3, B3, B6, B7 and B9). Since these revised documents still contain confidential information, the documents cannot be made publicly available. However, the information given can basically be found in the original draft assessment report together with the peer review report which both is publicly available.

THE ACTIVE SUBSTANCE AND THE FORMULATED PRODUCT

Metconazole is the ISO common name for (1*RS*,5*RS*;1*RS*,5*SR*)-5-(4-chlorobenzyl)-2,2-dimethyl-1-(1*H*-1,2,4-triazol-1-ylmethyl)cyclopentanol (IUPAC). The ISO name belongs to all possible ratios of the two pairs of diastereomers. However, it should be noted that the technical material used for the assessment has a certain minimum and maximum content of the isomers (see chapter 1).

Metconazole belongs to the class of conazole fungicides such as epoxiconazole, myclobutanil and triticonazole. Metconazole is taken up into crop leaves, and exhibits penetrant, local, and acropetal systemicity. Metconazole shows both curative and protectant properties and has demonstrated long term activity.

The representative formulated product for the evaluation was "Caramba 60 SL", a soluble concentrate (SL), registered in some EU Member States.

The conclusion was reached on the basis of the evaluation of the representative uses as fungicide as proposed by the applicant which comprises broadcast spraying to control foliar and ear diseases in

cereals and oilseed rape at application rate up 90 g metconazole per hectare. Metconazole can be used only as fungicide.

SPECIFIC CONCLUSIONS OF THE EVALUATION

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

Metconazole is a mixture of two pairs of diastereomers, the *cis*- and the *trans*-isomers[3]. It should be noted that the technical material used for the assessment has a certain minimum and maximum content of the isomers. The minimum purity of metconazole as manufactured should not be less than 940 g/kg (sum of *cis*- and *trans*-isomers), with "*cis*-metconazole" level not less than 800 g/kg and not more than 950 g/kg.
At the moment no FAO specification exists.

The technical material contains no relevant impurities.
However, since clarification is required with respect to certain impurities to confirm the proposed maximum levels in the technical material, the specification for the technical material as a whole should be regarded as provisional at the moment (some of the proposed maximum limits are above the concentration found in the respective "tox/(ecotox)" batches. The applicant has submitted recently studies to the RMS to address this issue. However, the addendum to B.6, December 2005, was neither peer reviewed by other Member States nor discussed in an experts' meeting. See also 2.8).
Beside this, the assessment of the data package revealed no particular area of concern.

The content of metconazole in the representative formulation is 60 g/L (pure).

The main data regarding the identity of metconazole and its physical and chemical properties are given in appendix 1.

Sufficient test methods and data relating to physical, chemical and technical properties are available. Also adequate analytical methods are available for the determination of metconazole in the technical material and in the representative formulation as well as for the determination of the respective impurities in the technical material.
Therefore, enough data 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 definition, i.e. metconazole in food of plant origin (cereals and oilseed crops only), soil, water and air.

[3] The c*is*-isomer is the 1*S*,5*R*/1*R*,5*S* pair and the *trans*-isomer the 1*S*,5*S*/1*R*,5*R* pair.

In contrast to the RMS, EFSA concluded that an MRL for food of animal origin (liver) might be necessary (see 3.2 and 3.4). Therefore an analytical method for the determination of metconazole in food of animal origin in particular for liver would be required. The available method was validated for milk, muscle, egg and fat, but not for liver. According to SANCO/825/00, an analytical method for liver is required, if an MRL is set or proposed.
Residues in food and soil can be determined with a multi-method (the German S19 method has been validated). For the other matrices only single methods are available to determine residues of metconazole.
The methodology used is GC with PN and MS detection. The latter is used as confirmatory technique.

The discussion in the experts' meeting (EPCO 25, May 2005) on identity, physical and chemical properties and analytical methods was limited to the specification of the technical material and some clarification with respect to physical properties of metconazole.

2. Mammalian toxicology

Metconazole was discussed at EPCO experts' meeting for mammalian toxicology (EPCO 23) in May 2005.

Metconazole technical is an 85:15% cis/trans mixture. Toxicological studies were performed with either the cis/trans or the cis isomer. For the two-generation study, only Metconazole cis was assayed, but according to the RMS, sufficient bridging data exist to justify this choice.

2.1 ABSORPTION, DISTRIBUTION, EXCRETION AND METABOLISM (TOXICOKINETICS)

Metconazole cis, is well absorbed (95-97% after 48h); after 48h, up to 83% of radioactivity is eliminated in the bile, while up to 12% is eliminated renally, by 72h about 93-96% of metconazole (cis/trans) is excreted.
Metconazole is widely distributed, but adrenals, gastrointestinal tract, and liver tended to have the highest amount of the compound. There is no indication that the metabolisation in the rat of the isomer mix is different than that of the cis-isomer. The major metabolites were recovered in the faeces. No significant difference was generally observed between sexes, except for M20 (1,2,4-triazole) mainly in female rats, and M12 (a carboxylated derivative) at a relative high proportion in the urine of males in all metabolism studies.
The parent compound was extensively metabolised as ≤2% of dose was recovered in the faeces. The metabolic breakdown was not affected by isomer ratio, sex, dose or pre-treatment.
The main metabolites of metconazole in rat are:
- monohydroxy-metabolites, (M1 and M21)
- hydroxyphenyl-metabolites (M15 and M19)
- carboxy-metabolites (M12 and M13)
- multi hydroxy metabolites (M18)
- mixed-function metabolites

- various sulphate conjugates of the abovementioned metabolites (M22)

Some plant metabolites (triazolyl alanine, its metabolite triazolyl acetic acid and M30, a keto-derivative of metconazole) are not present in rat metabolism. The experts discussed whether the information provided in JMPR review (Triazolyl alanine - Pesticide residues in food 1989 evaluations Part II Toxicology) was sufficient to determine the toxicological profile of triazolyl alanine (LD_{50}>5000 mg/kg bw, repeated dose study NOAEL 100 mg/kg bw/day, no genotoxic potential). The Member States agreed that it is less toxic than metconazole and asked EFSA to discuss with COM whether the data package of triazolyl alanine should be added to the dossier. No toxicological data is available on M30.

2.2 ACUTE TOXICITY

The acute oral toxicity of metconazole cis/trans is moderate (LD_{50} 595 and 410 mg/kg bw in rat and mouse, respectively). Therefore, a **classification Xn; R22** is proposed. The isomer-mix (cis/trans 85:15) is more toxic than the cis (95:5) isomer.

Metconazole cis/trans is of low acute dermal (LD_{50}>2000 mg/kg bw), inhalatory (LC_{50}> 5.6 mg/L) toxicity and it is not a skin or eye irritant or a skin sensitiser.

2.3 SHORT TERM TOXICITY

The short term toxicity of metconazole (both the isomer mix as the cis-isomer) was tested in subacute (rat, mouse, dog) and subchronic assays (rat, dog).

Metconazole cis/trans and metconazole cis induced a decrease in feed consumption and body weight, haematological disorders, increased transaminase activities (AST, ALT), gamma-glutamyl transpeptidase and alkaline phosphatase activity. Metconazole was shown to be a cytochrome P450-inducer. The effect was corroborated by liver weight increase and by histopathology (centrilobular hypertrophy). In addition, signs of liver necrosis and centrilobular vacuolation were observed.

Based upon liver effects, the relevant NOAEL was 6.4 mg/kg bw/day for metconazole cis/trans. Adrenals, liver and spleen were detected as target organs. In the dog, the subchronic toxicity profile was comparable with that observed in rodents, with liver and spleen effects at the top dose in both sexes. The cataractogenic potential of metconazole at the highest dose, after prolonged administration, was related to the interference with steroid biosynthesis of the substance.

2.4 GENOTOXICITY

The genotoxic potential of metconazole cis/trans 80/15 was investigated *in vitro* in the Ames test and in a chromosomal aberration assay in CHO cells, and *in vivo* in the mouse bone marrow micronucleus test and in an unscheduled DNA synthesis in rat liver cells. The genotoxic potential of Metconazole 95% cis was also investigated in a battery of tests both *in vitro* and *in vivo*. All the tests were negative with the exception of the chromosomal aberration assay performed with metconazole cis/trans: 80/15, where structural chromosomal aberrations were induced in the presence of S9-mix, in both main and repeat experiments. Overall, both metconazole cis/trans: 80/15 and metconazole 95% cis are not genotoxic.

2.5 LONG TERM TOXICITY

The administration of metconazole cis/trans (85/15) for 2 years to rats at a dietary dose of 45-55 mg/kg bw/day resulted in a minor (-5%) decrease in body weight at termination, and a slight increase in adrenal gland, liver and spleen weights. In the liver, severe vacuolation, and occasionally inflammatory or necrotic changes were reported. No neoplasms were observed. The increased incidence of hepatocytes with pigment deposit might be indicative of slight haemosiderosis, as subtle haematological disturbances were noted, and this finding was also reported in earlier studies. The observed increase in centrilobular hypertrophy had also been reported in the subchronic feeding study at the same dose-level, and was associated with the induction of CYP450-dependent metabolic enzymes. Based on a slightly increased incidence of adrenal cortical vacuolation, the NOAEL was determined at 4.3 mg/kg bw/day. In the mouse, similar toxicological endpoints were reported. At high doses, the compound was carcinogenic. Therefore, a NOAEL of 4.4 mg/kg bw/day was established for both chronic toxicity and carcinogenicity. Globally, as the tumours only appeared in the mice and not in the rat, and their emergence was explained by a Phenobarbital-like mechanism, and in the absence of genotoxic potential, it was considered by the experts a classification as a carcinogenic substance was not needed.

2.6 REPRODUCTIVE TOXICITY

At comparable dietary concentrations, the cis/trans mixture produced more maternal toxicity than the cis compound and at the cis isomer produced more toxicity to offspring than the mixture.

A 2-generation reproduction study in rats with the cis/trans isomer ratio is not available. The 2-generation study was conducted in rats with the metconazole cis isomer. The NOAELs for parental, reproduction and offspring toxicity were 8 mg/kg bw/day; based on the absence of effect on fertility in the rat 2-generation study (only modification of fertility parameters at maternotoxic doses), no classification for fertility was proposed.

Treatment of pregnant rats with the metconazole cis isomer resulted in maternal toxicity (clinical signs, decreased food consumption and bodyweight gain), embryo/foetotoxicity (increase in post-implantation loss, decrease in litter size, foetal weight, increase in placental weight) and skeletal ossification variations at the highest dose tested. The NOAEL for maternal and foetotoxicity toxicity was 24 mg/kg bw/day. At this and higher doses, an increased incidence of bilateral hydroureter was observed at necropsy. Thus, the developmental NOAEL was established at 6 mg/kg bw/day.

Both compounds were embryo- and foetotoxic at doses also producing maternal toxicity in rat developmental toxicity studies. Overall, the weight of evidence is that technical metconazole is embryo/fetotoxic in rats and rabbits at doses associated with maternal toxicity and has shown some evidence of teratogenic potential in rabbits at doses producing no to severe maternal toxicity.

Therefore, classification as Reproductive toxicant **Cat. 3 (Xn; R63 "Possible risk of harm to the unborn child")** was agreed during the meeting.

2.7 NEUROTOXICITY

No studies were conducted.

2.8 FURTHER STUDIES

The metabolite AC382390 (M11), 91.5% pure, was found to produce low acute toxicity after oral administration to rats (LD_{50} > 5000 mg/kg).

Genotoxicity studies on impurities 3 and 7 (CL354282 and CL 357625) have been presented in an addendum submitted by the RMS in a late stage of the process. Therefore, results were not peer reviewed.

2.9 MEDICAL DATA

There have been no reports on health-related adverse effects, caused by exposure to metconazole technical or formulation handling.

2.10 ACCEPTABLE DAILY INTAKE (ADI), ACCEPTABLE OPERATOR EXPOSURE LEVEL (AOEL) and ACUTE REFERENCE DOSE (ARfD)

ADI

The overall NOAEL of 4 mg/kg bw/day (accounting for long term, reproductive and subchronic effects), was considered relevant for setting an ADI.

In the light of the teratogenic effects, an additional assessment factor of 4 was agreed on by the experts, in order to obtain a sufficient margin of safety (1000 x) compared to the dose-level were the effect was observed. Therefore, with a NOAEL of 4 mg/kg bw/day, and a safety factor of 400, **the ADI is 0.01 mg/kg bw/day.**

AOEL

The AOEL is 0.01 mg/kg bw/day, based on the overall NOAEL of 4 mg/kg bw/day with a safety factor of 400 (extra factor of 4 due to teratogenic effects).

ARfD

As teratogenic effects were detected in the rabbit studies at 4 mg/kg bw/day, it is proposed to establish an acute reference dose on this basis. Taking into account a SF of 400, the value of 0.01 mg/kg bw/day was set.

2.11 DERMAL ABSORPTION

Dermal absorption of metconazole have been assessed through one *in vivo* dermal absorption study in rats and a comparative *in vitro* study (human skin) with metconazole formulated as Caramba 60 SL. Values of 4% for the concentrate and 65% for the dilution were agreed during the meeting.

EFSA note: a new *in vivo* study has been conducted by the applicant with an interim report showing lower values; since the study was not peer reviewed by the experts, data from this study were not taken into consideration. It could be used at Member State level.

2.12 EXPOSURE TO OPERATORS, WORKERS AND BYSTANDERS

The representative plant protection product Caramba 60 SL is an SL formulation containing 60 g/L pure metconazole, to be used as fungicide in cereals (wheat, barley, oats, rye, triticale) and oilseed rapes (application rate 0.09 kg as/ha).

Operator exposure

According to the UK POEM operator exposure model, the estimated exposure to metconazole is higher than the AOEL, formulated as Caramba 60 SL, both with or without gloves during any task. When operator exposure was estimated using the German model it was observed that exposure exceeded the AOEL in the absence of PPE, but that it was lower than the AOEL when gloves, coveralls and boots would be worn during the operations.

Scenario	Model	No PPE	With PPE*
Field crops, hydraulic nozzles	**German model**	366%	25%
	UK POEM	2110%	323%

*UK-POEM: gloves during mixing/loading and application

German model: gloves during mixing/loading and application, coverall and boots

Worker exposure

The exposure during re-entry activities in cereals, is low and accounts for the 2.44% of the AOEL.

Bystander exposure

Exposure for bystanders at 7.5 m distance in a field crop treated with metconazole is negligible (< 1% of the AOEL).

3. Residues

Metconazole was discussed at EPCO experts' meeting for residues (EPCO 24) in May 2005. The RMS did not attend the discussion.

3.1. NATURE AND MAGNITUDE OF RESIDUES IN PLANT

3.1.1. PRIMARY CROPS

Plant metabolism was studied in wheat and oilseed rape following foliar application of metconazole radiolabelled in two positions. Metconazole and the metabolites triazolyl alanine and triazolyl acetic acid as well as the stereoisomeric monohydroxy metabolites M11/M21 were identified as the major components of the total residue in plant parts at harvest. Triazolyl alanine and triazolyl acetic acid

accounted for the major residue compounds in wheat grain (*ca* 33% and 9% TRR, respectively), while parent metconazole was minor (<2% TRR). In contrary, in wheat straw metconazole made up the majority of the total residue (*ca* 32%TRR), and the monohydroxy metabolites M11/M21 (each *ca* 10% TRR) were also major. In seeds of oilseed rape, metconazole was a major constituent (up to 39% TRR) besides triazolyl alanine (*ca* 40% TRR), while in foliage and pods besides metconazole (*ca* 17-60% TRR) the monohydroxylated compounds and their glucose conjugates were dominating (up to *ca* 65% TRR).

In both crops studied, the primary metabolic pathway of metconazole proceeds by oxidative hydroxylation of the benzylic methylene group, the methyl side chain on the cyclopentyl ring, and potentially the cyclopentyl ring to produce monohydroxylated metabolites of metconazole which are further conjugated through glycosidation. The presence of triazolyl alanine and its acetic acid derivative suggested that the methylene group between the triazole ring and the cyclopentyl ring is also susceptible to oxidative hydroxylation. Triazolyl alanin, derived from 1,2,4-triazole and the o-acetyl-serine by cysteine synthases, was very well translocated and mainly detected in the non vegetative parts of plants in which it was stored.

Alltogether, the metabolic pathway of metconazole in plants can be considered as sufficiently investigated, and all the identified metabolites were covered by toxicological data. (see 2.1 and 2.8)

Therefore, the residue definition for risk assessment and for compliance with MRLs is proposed as metconazole. Due to the fact that the investigation of the metabolic behaviour of metconazole in plants is limited to oilseed crops and cereals, a final residue definition for plants in general cannot be proposed.

A range of supervised residue trials have been conducted with metconazole in open field conditions on wheat, barley, rye, triticale and oilseed rape in accordance with the cGAP. The trials were reported in sufficiently detail and were supported by acceptable analytical information. Metconazole was the residue determined in all trials. In some residue trials, also the metabolite triazolyl alanine was determined, but was not considered in the evaluation. A complete set of trials from Northern and Southern Europe was submitted for wheat, allowing for extrapolation to rye and triticale. Metconazole residues in grain in those trials were mainly below the LOQ (0.02 mg/kg) with few exceptions amounting to 0.05 mg/kg. In barley grain, where initially no trials for the south were submitted, residues amounted to 0.09 mg/kg. Again, extrapolation to oat was considered possible. However, data are currently not complete to fully support uses in barley and oat in Southern Europe. This was not altered by the later submission of four residue trails on barley in the south, which are evaluated in an addendum (August 2004). In oilseed rape trials in Northern and Southern Europe a maximum residue in seeds of 0.11 mg/kg was found.

The nature and magnitude of metconazole residues after processing has not been assessed. Based on the representative uses for Annex I inclusion processing studies are not required, since the TMDI is below 10% ADI (see 3.3).

3.1.2. SUCCEEDING AND ROTATIONAL CROPS

A confined crop rotation study with radio labelled metconazole was conducted to address the potential incorporation of soil residues into succeeding crops. Metconazole was applied to soil at a rate of 0.4 kg a.s./ha (*ca* 2 N) and aged in the soil for either 30 or 120 days before planting lettuce, radish and wheat. The total radioactive residues seem slightly to increase with the planting interval, and total radioactivity (as metconazole equivalents) amounted to 0.71 mg/kg in radish root, 0.20 mg/kg in lettuce foliage and 0.49 mg/kg in wheat grain in the test with triazole-^{14} C labelled material. The study indicated that unchanged metconazole was uptaken from the soil, since it was present in all crops tested. Major compounds in all crops were also the metabolites triazolyl alanine and triazolyl acetic acid, as well as M12 in radish. With time, levels of metconazole appeared to be constant in the respective crop parts, and no accumulation of metconazole is expected in rotational crops. Thus the slight increase of total radioactivity with time may be attributed to increased uptake of metabolites from soil. Altogether, the study showed a comparable metabolic pattern in succeeding crops as in directly treated plants. Thus, only metconazole is the relevant residue in succeeding crops.
In a field study carrots, lettuce and wheat were planted following metconazole application to bare soil at a rate corresponding to cGAP (twice 0.09 kg a.s./ha). The replanting interval was 30 days (carrots, lettuce) and 98 days (wheat), respectively. Metconazole was the residues determined in the trial. At harvest, residues in the plant samples were all below the LOQ (0.01mg/kg; straw 0.03 mg/kg). In this study the enrichment of plant parts of leafy vegetables, root vegetables and cereals, installed as succeeding crops, with metconazole was not sufficient to reach quantifiable levels. Based on that data, no significant residue levels are expected in rotational crops following application of metconazole according to cGAP.

3.2. NATURE AND MAGNITUDE OF RESIDUES IN LIVESTOCK

Livestock metabolism was studied in dairy goats and laying hens by orally dosing the animals with ^{14}C-metconazole. Administered metconazole was rapidly metabolised and excreted. Hence radioactivity was mainly found in goat urine (33-44% of total dose) and faeces (28-46%), and in hen excreta (92%), respectively. Excretion in milk and eggs was comparatively minor and TRR in milk and eggs plateaued within 4 and 8 days of dosing, respectively. It is noted that with regard to its logPow metconazole is characterised as fat soluble (log Pow 3.85). However, TRR were roughly one order of magnitude higher in the excretory organs liver and kidney of both species than in other animal tissue, indicating that there might be no accumulation of residues in adipose tissue.
Chromatographic analysis of goat matrices show that metconazole made up the majority of the residue in liver, fat and muscle tissues, while it was hardly detected in kidney and urine samples (<2%TRR). Therein, monohydroxy metabolites M1 (up to *ca* 26% TRR) and M31 (up to *ca* 35% TRR)) and the carboxylic acid metabolite M12 (*ca* 20% TRR) were the major constituents. Results from the goat studies suggest that metconazole is rapidly and completely metabolised through oxidative processes, forming monohydroxylated compounds, which are further oxidized to carboxylic acid metabolites and/or conjugated subsequently. All metabolites identified in goat tissues were also found in the rat metabolism.

In laying hens, no metabolic pathway was established since in the submitted study no further characterization of the recovered radioactivity in hen matrices was attempted. Since the intake by poultry is not significant in terms of the representative uses, no further data are currently required.
Based on the information gained from the goat studies the residue definition in animal matrices for risk assessment and for compliance with MRLs is proposed as metconazole.

In the residues experts' meeting it was concluded that due to the additional, more critical residue data on barley the dietary burden for livestock had to be reassessed and depending on the result the submission of livestock feeding studies might be necessary. A reassessment of livestock dietary burden was submitted by RMS in an addendum after the final discussion of metconazole in the evaluation meeting (addendum December 2005). This revised assessment is however not agreed by EFSA since for beef cattle intake from residues in straw has not been considered as requested by EPCO 24. An estimation of the dietary burden of beef cattle and the expected metconazole residue levels in ruminant edible matrices provided in the EFSA addendum of January 2006 indicates that for ruminant liver the trigger value of 0.01 mg/kg is exceeded. According to current guidelines a feeding study would be required. Moreover, MRLs for food of animal origin may need to be proposed. However, the exceedance of 0.01 mg/kg only concerns ruminant liver and there are two metabolism studies with ruminants available. These studies are carried out at different dose levels but lead to a similar outcome. Thus, extrapolation could be used to estimate the residue level occurring in ruminant liver at 1N feeding rate and to propose an MRL. The estimated metconazole residues in beef liver amount to 0.019 mg/kg. Taking into account that such extrapolation from studies carried out at exaggerated doses may result in some uncertainty, a provisional MRL of 0.05 mg/kg for ruminant liver is proposed. However it is up to the applicant to submit further data (e.g. a feeding study) showing that quantitative transfer of metconazole residues to ruminant liver would be much lower than currently estimated from metabolism studies. It is noted that an analytical method for monitoring and enforcement purposes for liver still needs to be validated. (refer to chapter 1) However, it is stressed that these aspects were neither peer reviewed nor discussed by experts and therefore further consideration is needed.
For poultry it appears that no significant residues are expected in poultry products, and hence no feeding study in poultry was required. No metabolism and feeding studies with metconazole were triggered for pigs.

3.3. CONSUMER RISK ASSESSMENT

The chronic dietary risk assessment for consumers is based on information obtained from residue trials in cereals and oilseed rape and on European and international consumption data. It is noted, that potentially occurring residues in food of animal origin haven't been considered in these estimates.

The theoretical maximum daily intake (TMDI) for an adult based on the WHO model (GEMS/Food European diet) was less than 4% of the proposed ADI. National Estimates of Daily Intake (NEDI) were calculated for UK consumers with the UK Rees/Day model (Two highest 97.5th percentile intakes plus mean intakes from other food). Total intakes for all considered consumer groups were all

well below the ADI of 0.01 mg/kg bw/day, accounting for *ca* 3%, 6% and 7% of the proposed ADI for adults, children and infants, respectively.
The acute dietary risk assessment showed that the National estimated Short Term Intake (NESTI), using the UK model for adults and toddlers, is well below (15 %) the ARfD of 0.01 mg/kg bw/day.

The dietary risk assessment performed for different consumer groups indicates that there are no chronic and acute concerns related to dietary exposure resulting from the representative uses. Contribution of consumer intakes of residues from food of animal origin (ruminant liver) is expected to be negligible (<1% ADI and ARfD, respectively).

3.4. PROPOSED MRLS

Based on the representative uses evaluated for Annex I inclusion of metconazole and the proposed residue definition the following MRLs are proposed:

Wheat, rye, triticale	0.05 mg/kg
Barley, oat	0.1 mg/kg
Rape seed	0.2 mg/kg

It is noted that currently no sufficient data is available to fully support the MRL proposal for barley and oat for Southern European uses. (see 3.1.1)

The RMS is of the opinion that representative uses do not give rise to significant residues in animal products and MRLs do not need to be proposed. (see RMS addendum December 2005)
In contrast, EFSA concluded that an MRL proposal for ruminant liver might be necessary (see EFSA addendum January 2006). Accounting for uncertainties when extrapolating from figures obtained after exaggerated dosing in livestock metabolism studies, the following MRL for food of animal origin is proposed:

Ruminant liver	0.05 mg/kg

The proposal is provisional and might be revised upon receipt of precise information on quantitative transfer of metconazole residues to edible animal matrices.

Metconazole is approved in non-European countries, but no Codex (CAC) MRLs have been established or proposed yet and need to be considered.

4. Environmental fate and behaviour

Issues raised during the peer review were discussed in a scientific meeting of Member State experts in April 2005 (EPCO 21).

4.1. FATE AND BEHAVIOUR IN SOIL

4.1.1. ROUTE OF DEGRADATION IN SOIL

In a laboratory (dark aerobic 20°C and 50% maximum water holding capacity (MWHC)) study carried out on a sandy loam soil dosed with 3,5-triazole-^{14}C-metconazole, mineralization to CO_2 was low but represented 4.8 % of applied radioactivity (AR) at 91 days (10.3%AR at 120 days). Radioactivity not extracted using acetonitrile/water accounted for 27%AR at 91 days (39.2%AR at 120 days). In soil extracts chromatography identified slow formation of CL 382389[4] but this metabolite accounted for a maximum of 4.6%AR at 91 days, no other resolved components in extracts were identified, none accounted for more than 2.96%AR at any sampling time. In experiments in 5 further soils (dark aerobic 20°C and 40% MWHC) where volatiles were not trapped, that were dosed with cyclopentanol-^{14}C-metconazole, radioactivity not extracted sequentially with acetonitrile/water, acetonitrile and diethylether accounted for 12-28%AR at 112 days. No resolved components in extracts were identified, none accounted for more than 4.2 %AR at any sampling time.

Under dark anaerobic conditions in the laboratory (20°C, studied in a sandy loam soil, dosed with 3,5-triazole-^{14}C-metconazole) the metabolite CL 382389 was formed at only 0.59%AR, no other resolved unidentified components in extracts accounted for >1.13% AR. Mineralization to CO_2 was minimal 0.26%AR at 120 days and the formation of residues not extracted by acetonitrile/ water were lower (8.6%AR at 120 days) than under aerobic conditions.

In Laboratory soil photolysis studies where 3,5-triazole-^{14}C-metconazole was used as test substances the rate of breakdown of metconazole was faster than in dark controls, however no novel breakdown products were identified and no chromatographically resolved breakdown product in soil extracts accounted for > 6.7% AR.

4.1.2. PERSISTENCE OF THE ACTIVE SUBSTANCE AND THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

In dark aerobic laboratory studies (20-22°C and 40-50% MWHC) single first order DT_{50} were estimated to be 84-598 days although results for 5 of the 6 soils tested are extrapolated 1.7-5.3 times the duration of the experiments (112 days). This range after normalisation to field capacity soil moisture content (-10kPa) and 20°C was by coincidence the same (84-598 days, mean 220 days).

The results of field dissipation studies (bare soil study design) at 10 European field trial sites (8 in Northern Europe: UK and Germany and 2 in Southern Europe: France) are available[5]. Member State experts discussed these field dissipation studies and concluded that they did not provide reliable estimates of the degradation of metconazole under field conditions. The main reasons for having reservations regarding the use of these studies to determine estimates of field degradation were:

[4] CL 382389: (2-Hydroxy-3,3-dimethyl-2-[1,2,4]triazol-1-ylmethyl-cyclopentyl)-(4-chlorophenyl)-methanone

[5] These trials were summarised briefly in section B.8.1.3.1 of the DAR and summarised more completely in Annex B to Volume 3 of the DAR.

1. that the number of soil samples that were analysed from soil depths deeper than 10 or 15 cm was limited to a few sampling times generally at later sampling times in the studies and
2. the relatively high limit of quantification (LOQ) of the method of analysis used (0.01mg/kg, validated limit with acceptable procedural recoveries) relative to the initial or highest concentrations measure in soil shortly after application at some trial sites (lowest, 0.06mg/kg highest, 0.52mg/kg). The LOQ therefore represents 1.9-16% of the maximum measured residue in the trials.

Therefore movement to deeper soil layers could not be excluded as a route of dissipation in these field trials (downward movement cannot be excluded but would probably have been fairly limited based on the evidence from laboratory batch adsorption measurements for metconazole, see section 4.1.3). The EFSA agrees with these reservations regarding using the trials to provide soil degradation rates, but considers the field trials do provide reliable estimations of the dissipation rate of metconazole from the top soil layers in the field, accepting that in all trial sites it would not have been possible to measure a soil concentration that was equivalent to the theoretical DT_{90} concentration. The EFSA therefore considers it appropriate to use the DT values from these field trials to estimate potential top soil accumulation, and PEC in the top soil layer. The reasoning behind this conclusion is that dissipation to deeper soil layers, if it occurs, would reduce concentrations that organisms living in soil are exposed to, so these risk assessments would not be compromised. The results of the field studies should not however be used as input to FOCUS modelling or any other assessment that needs a degradation rate (and not a dissipation rate) as input.

In the two Southern European field studies and 4 of the Northern European field studies the residues of the pair of cis diastereoisomers were determined and reported separately from the pair of trans diastereoisomers (cis and trans isomers were resolved by the chromatographic methods). There was no change of the cis/trans ratio from that of the test substance applied, at the different sampling times. (Note the stereoisomer pairs were not resolved by the methods used, i.e. chiral chromatography was not used).

Single first order field dissipation DT_{50} from the top 10-15cm soil layer for Northern Europe were calculated to be 70-259 days (DT_{90} 238-854 days) at 5 trial sites. $\sqrt{1}^{st}$ order field dissipation DT_{50} from the top 10cm soil layer for Northern Europe were calculated to be 33-40 days (DT_{90} 363-442 days) at a further 3 trial sites. Single first order field dissipation DT_{50} from the top 15cm soil layer for Southern Europe were calculated to be 49-154 days (DT_{90} 168-504 days) 2 trial sites.

It should be noted that application dates in the field studies were in May and June which will probably reflect application timings of the uses considered in this dossier for annex 1 listing in most years. The DT values derived from these field studies should not be used to support early spring, late autumn or winter applications of metconazole without further assessment and manipulation of the DT values from the trials to account for lower soil temperatures at these times of year.

A field accumulation study (cropped with autumn sown cereals) was carried out at one site in the UK[6] This study that had applications made in May and June every year (i.e. 2 per year) to the developing crop canopy at the representative cereal use application rate (0.09kg a.s./ha) included incorporation of chopped cereal straw into soil in the last 3 years of the study (so included the addition of metconazole plant residues to soil). In this study residues had returned to <0.01 mg/kg (LOQ) in the 0-10cm top soil layer every year before the new seasons first application was made. Therefore at this trial site accumulation did not occur. The trial site was different from the UK sites where field dissipation studies had been carried out. Reliable DT_{50} at this study site cannot be estimated from the data due to low initial concentrations measured in soil after applications (which were to canopy foliage) and the limited number of samples taken in the decline phase (3). A rough estimation of the single first order dissipation DT_{50} at this accumulation trial site would be around 120 days. This is within the range of values seen in the field dissipation studies but dissipation at some trial sites was significantly longer than this. The EFSA therefore considers the potential for accumulation cannot be discounted based on just the evidence from this one UK field accumulation study. PEC in soil were therefore appropriately calculated by the RMS using the longest field DT_{50} (single first order 259 days) for applications in successive years to produce calculated accumulated levels for use in risk assessment (section B.8.3 of the DAR). The EFSA considers Member States should use the same approach and calculate accumulated levels when considering national authorisations for additional uses on other crops or different application rates on cereals and oilseed rape to those applied for as the intended uses for annex 1 listing.

4.1.3. MOBILITY IN SOIL OF THE ACTIVE SUBSTANCE AND THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

In guideline laboratory batch adsorption studies on 9 soils metconazole $K_f$oc were determined in the range 726-1718mL/g (mean 1116mL/g, median 1019mL/g) with corresponding 1/n values in the range 0.666-1.02 (mean 0.88). There was no indication of adsorption being pH dependant as would be expected for a substance with pKa values (acid dissociation constants) of 11.38 and 1.08.

4.2. FATE AND BEHAVIOUR IN WATER

4.2.1. SURFACE WATER AND SEDIMENT

Metconazole was stable to hydrolysis. In 2 laboratory aqueous photolysis studies (one in sterile buffer the second using a natural water), Single first order DT_{50} under continuous artificial test system irradiation (light radiation energy not equated to natural sunlight conditions) at pH 7- 8 and 22-25°C were 36 and 58 days. In the sterile study the metabolite CL395834[7] was formed at 14.5%AR after 30 days. In the natural water study no breakdown product accounted for > 6.4%AR. In the natural water study breakdown products were characterised as polar but were not identified. Half lives calculated for a 1 m deep natural surface water at 20°C with no suspended solids using the quantum yield and a

[6] This study was summarised briefly in section B.8.1.3.1 of the DAR and summarised more completely in Annex B to Volume 3 of the DAR. This summary includes tables with the residue results at all sampling points in every year of this 6 year study (as requested by the meeting of fate experts).
[7] hydroxymetconazole

June day of 16.5 hours at 40°N using the methods of Frank and Klopffer[8] was at least 7397260 years. Therefore the EFSA considers that under natural surface water conditions, photolysis would not be expected to be a process that contributed significantly to the degradation of metconazole and the metabolite CL395834 is unlikely to be present at significant concentrations in real field situations.

In 2 natural sediment water systems studied in the laboratory in the dark at 20°C (6cm water column overlying 2-2.5cm sediment) 3,5-triazole-^{14}C-metconazole dissipated from the water by partitioning to sediment with single first order DT_{50} of 1-15 days. These values for the whole systems were 116-814 days. The 3,5-triazole-^{14}C-label, did not mineralize to CO_2 in either test system (no radioactivity recovered from volatile traps over the 182 day experiment). Radioactivity not extracted from sediment using sequentially acetonitrile/water, acetonitrile and diethyl ether was 11-19%AR at 100 days (14-19%AR at 182 days). 5 metabolites were identified but none accounted for > 9%AR in the water phase or >5.2%AR in the sediment phase at any sampling time. The most prominent water metabolite was CL 359139[9] which was present at up to 9%AR at day 152 but had a slightly lower measured level of 8.5%AR at day 182. Unidentified radioactivity always accounted for < 8%AR in either the water or sediment phases and in the opinion of EFSA there was no clear trend in the available studies of the amount of unidentified residue increasing (concentrations measured at 182 days were generally lower, or about the same as those measured at 152 days). It is a concern that from the satisfactory standard guideline studies required and provided, in terms of the material balance of metconazole in aquatic systems, the EFSA can conclude little more than metconazole is persistent in such systems. All that can be concluded about the fate and behaviour in static aquatic systems is that metconazole moves out of the water column relatively rapidly by partitioning to sediment with the only significant sink for the decline of metconazole being the formation of unextracted sediment residues. Whilst some metabolites were formed, their levels were low and they did not mineralize to CO_2

Appropriate predicted environmental concentrations in surface water systems due to contamination via spray drift were calculated for parent metconazole for a 30 cm deep static water body for the evaluated representative uses. These values as calculated by the rapporteur in the DAR were endorsed by the meeting of experts as representing a reasonable worst case for the spray drift route of entry. Whilst an assessment of exposure to surface water from the runoff and drainage routes of entry was considered in the DAR (Through the use of FOCUS surface water step 2 calculations), the selection of input parameters used in the calculations was not appropriate (the dissipation DT_{50} of 15 days from the water phase was used as input whilst this calculation approach requires a water degradation rate to be used). Also the PEC in sediment calculated with the step 2 FOCUS calculator, did not take account of the potential accumulation from use in successive years. The runoff and drainage routes of exposure to surface water have therefore not been considered in an agreed EU level exposure

[8] Frank, R. & Klopffer W. Ecotox. Environ. Safety 17 (1989) 323-332, and Frank, R. & Klopffer, W., Battelle-Institute. V. Frankfurt, Report No. 106 02 046/BF-R-66 105 for the Umweltbundesamt, Berlin 1985.
[9] 3-(4-Chlorobenzyl)-2-hydrooy-1-methyl-2-[1,2,4]triazol-1-ylmethyl-cyclopentane-carboxylic acid

assessment and should be considered at Member State level and where pertinent additional aquatic risk assessments completed.

4.2.2. POTENTIAL FOR GROUND WATER CONTAMINATION OF THE ACTIVE SUBSTANCE THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

Appropriate FOCUS groundwater modelling for parent metconazole was carried out to cover the representative uses applied for, for annex 1 listing at all 9 standard FOCUS groundwater scenarios using FOCUSPELMO 3.3.2. This modelling is described in the addendum to the DAR dated September 2005. Taking account of the complete data base of studies, the main pesticide properties appropriate for use as input to the modelling according to FOCUS guidance would be a mean laboratory single first order degradation DT_{50} at 20°C and -10kPa of 220 days and the mean adsorption parameters being a $K_f oc$ of 1116mL/g and 1/n 0.88. The actual parameters used in the modelling were similar to these but actually result in more worst case leaching estimates for parent metconazole (slightly longer single first order DT_{50} of 247 days, slightly lower adsorption $K_f oc$ 1000mL/g 1/n 0.94). Annual average leachate concentrations leaving the top 1m soil layer for the representative uses applied for, for annex 1 listing were predicted by the model to be <0.1µ/L for all the FOCUS scenarios (highest value predicted was 0.023µ/L for use on winter cereals at the Piacenza scenario).

The results of this modelling indicate that over a broad range of geoclimatic conditions in Europe, contamination of vulnerable groundwater resources above the parametric drinking water limit for individual pesticides of 0.1µg/L is considered unlikely, when products containing metconazole are applied in accordance with the representative uses assessed in this conclusion.

4.3. FATE AND BEHAVIOUR IN AIR

Volatilisation of metconazole from soil and bean leaves was investigated in a BBA guideline study under controlled indoor conditions

After 24 hours >86% of the applied metconazole remained on the sandy soil substrate and >87% was recovered from the bean leaves. Therefore, volatilisation losses from these substrates are likely to be relatively low, as the losses measured are within the variability of the study design (recovery of time 0 samples was 87-95% of applied).

Metconazole has a low vapour pressure ($2.1x10^{-8}$ Pa at 20°C) and its Henry's Law constant $2.21x10^{-7}$ $Pa.m^3.mol^{-1}$ indicates it would not be expected to volatilise from aqueous systems.

The DT_{50} of metconazole in the atmosphere due to photochemical oxidative degradation in the presence of hydroxyl radicles was calculated using the method of Atkinson to be 6.5 hours assuming an atmospheric hydroxyl radical concentration of $1.5x10^6$ OH radicles cm^{-3}. Therefore any metconazole that did reach the upper atmosphere would not be expected to subject to long range transport.

5. Ecotoxicology

Metconazole was discussed at the EPCO experts` meeting for ecotoxicology (EPCO 22) in April 2005.

5.1. RISK TO TERRESTRIAL VERTEBRATES

The RMS provided in the DAR a first tier risk assessment according to SANCO/4145/2000. The acute and short-term risk assessments for birds lead to TER values higher than the relevant Annex VI trigger of 10 for both representative uses. The long-term TER values for birds (2.3 to 3.1) did not exceed the Annex VI trigger of 5. A refined risk assessment to address the long term risk to herbivorous and insectivorous birds was presented in the revised DAR from January 2005. The use of yellowhammer (*Emberiza citrinella*) and marsh warbler (*Acrocephalus palustris*) as focal species was questioned in the experts' meeting. According to the information submitted by the applicant they spend only 2 % and 2.7 % of their time in the treated area. The meeting decided that the applicant should present data on more species to refine the risk assessment for insectivorous birds and to submit further argumentation supporting the use of yellowhammer and marsh warbler as focal species. The meeting agreed that an interception factor cannot be used as a refinement step for insectivorous birds since interception is already taken into account in the default RUD values for insects. This is not corrected in the revised DAR from September 2005. The long term risk to herbivorous birds was refined by using residue data in cereals. The RUD refinement was confirmed by the meeting. The long-term risk to herbivorous birds is considered to be low from the representative uses. Further data are required to address the long-term risk to insectivorous birds for the representative uses in cereals and oilseed rape.

The first tier risk assessment for mammals resulted in TER values exceeding the relevant Annex VI trigger values for the acute risk from both representative uses. The long term TER value of 5.3 for the representative use in oilseed rape met the Annex VI trigger but not the long-term TER for herbivorous mammals in cereals (TER = 0.57). In the refined risk assessment a RUD value of 20.75 was used which was based on residue data in cereals. This refinement step was accepted by the experts' meeting. However, the resulting TER value of 2.9 is below the Annex VI trigger of 5. Some further refinement steps are necessary to address the risk to small herbivorous mammals for the representative use in cereals. The acute and the long term risk to mammals from the representative use in oilseed rape are considered to be low.

The risk to birds and mammals from secondary poisoning from uptake of contaminated earthworms was discussed at the experts' meeting. It was agreed that the TER calculations should be based on the plateau PECsoil plus one application. The resulting TER values for birds and mammals of 10.5 and 5.3 are above the Annex VI trigger of 5 indicating a low risk from the representative uses.

No risk assessment for the uptake of drinking water was available. It is not clear whether exposure to contaminated drinking water can be excluded for the representative uses of metconazole. Therefore

EFSA calculated in an addendum the TER values according to Sanco/4145/2000. The acute TER values for birds and mammals exceeded the relevant Annex VI trigger values but the short-term and the long-term TER values for birds and the long-term TER values for mammals were below the Annex VI trigger values indicating a high risk. A refined risk assessment for the uptake of contaminated drinking water is required for the intended uses in cereals and oilseed rape.

A high risk from contaminated drinking water was shown from a first tier risk assessment based on worst case assumptions (e.g. the total daily water demand is taken from leaf axils or puddles which are contaminated by the sprayed solutions). Some Member States are of the opinion that long-term exposure to contaminated drinking water can be excluded and hence regard the long-term risk from uptake of contaminated drinking water as low. However, no common agreement among Member States exists yet on the potential long-term risk from contaminated drinking water. It is planned to discuss the risk to birds and mammals from uptake of contaminated drinking water as a general point in an EPCO experts' meeting.

5.2. RISK TO AQUATIC ORGANISMS

The acute toxicity to the tested fish, daphnia and algae was in the range of 1.7 – 4.2 mg a.s./L. The meeting discussed the setting of the 21 d NOEC value to 0.16 mg a.s./L for *Daphnia magna* , study of Jatzek, 2002 with the technical active substance. The meeting agreed to accept the endpoint if the statistical analysis clearly shows that the variability in the controls is low. RMS checked the statistics and confirmed the setting of the NOEC at 0.16 mg a.s./L.

The study with *Chironomus riparius* was discussed in the experts' meeting. Since only the concentration of the active substance in the water phase was measured it was questioned whether the result can be used for the risk assessment. In the corrigendum of September 2005 (not peer reviewed) the RMS multiplied the NOEC of 2.12 mg a.s./L (based on the measured concentration in the water phase) by 10 to extrapolate to the NOEC of 21.2 mg a.s./kg sediment. This extrapolation was based on the water to sediment volume ratio in the *Chironomus* test of 10:1. The TER from the NOEC of 21.2 mg a.s./kg sediment and a PECsed plateau concentration of 0.12 mg a.s./kg sediment for sediment dwelling organisms was calculated to be 177. The extrapolation of the RMS is based on the assumption that the whole amount of active substance in the test system with *Chironomus* shifted from the water phase to the sediment phase. No reasoning is given in the corrigendum to support this assumption. EFSA is of the opinion that the assumption that 100% partitioning of active substance to sediment would have occurred in the 28 day *Chironomus* study (with a water to sediment ratio of 10:1) is not appropriate.

In the fate and behaviour sediment water study for the pond system (organic carbon content of the sediment most closely matches that of the *Chironomus* test system), that had a water to sediment ratio of 3:1 (i.e. greater potential for partitioning to sediment), at 30 days only 65% of the test substance applied to the system was present as metconazole in sediment. Therefore the EFSA proposes that the accumulated maximum PEC in sediment from the representative uses of 0.14mg a.s./kg wet weight sediment, should be expressed as an equivalent water concentration using the water to sediment ratio

of the *Chironomus* study. In the *Chironomus* test system there was 1800mL of water and 0.239kg wet weight of sediment (assuming a wet sediment density of 1.3g/mL for the sediment volume in the test systems of 184mL). Therefore the water concentration in the *Chironomus* study equivalent to 0.14mg a.s./kg wet weight sediment, assuming 65% partitioning to sediment is 0.0286mg/L. Therefore, the TER for sediment dwellers taking account of potential accumulation in sediment is 2.12/0.0286 = 74. The risk to *Chironomus riparius* is expected to be low.

Daphnids were significantly more sensitive to the formulation than to the technical a.s.. The RMS conducted a risk assessment based on endpoints deriving from toxicity tests with the technical active substance and the formulation. The initial spray drift PECsw concentrations for the active substance and the formulation were compared to the endpoints from the toxicity tests with the active substance and the formulation. The lowest endpoint was derived from an early life stage test with the technical active substance and *Oncorhynchus mykiss* (95 d NOEC = 0.00291 mg a.s./L). The resulting chronic TER for fish was calculated for a buffer zone of 5 m to be 11.78. Therefore the risk to fish is expected to be low if a buffer zone of 5 m is applied.
It was discussed in the experts' meeting whether the 21 d static renewal test with the formulation and *Daphnia magna* should be used for the risk assessment. The EPCO meeting agreed that the endpoints from studies with the formulation under static renewal conditions should be used in the risk assessment since this represents a worst case assumption for entry into surface water via spray drift. The applicant commented that a chronic study with static renewal or flow through conditions would significantly overestimate the risk because the higher toxicity of the formulation is due to the formulant "neodol" which is readily biodegradable under natural conditions. A chronic study under static test conditions which should confirm this argument was stated by the applicant to be available. The meeting set a data requirement for the applicant to submit the study. Based on the endpoint from the study under static renewal conditions a buffer zone of 15 m is required to achieve a TER value of 13.65 which is above the Annex VI trigger of 10. The new 21 d chronic study with *Daphnia magna* could be taken into account for the risk assessment at Member State level.

The metabolite CL 359139 reached a maximum of 9 % of the AR after 152 days. It is not clear from the environmental fate data if the concentration of CL 359139 is decreasing or remains at a level close to 10 % of AR. In order to pose a higher risk to aquatic organisms than the parent, the metabolite would have to be 10 times more toxic than metconazole. This is considered as unlikely since the structure is similar to metconazole and the only difference is the formation of a carboxylic acid group. The carboxylic acid group would make it more water soluble and easier for organisms to excrete. Therefore the risk from the metabolite CL 359139 is expected to be lower compared to metconazole.

It is concluded that the acute risk to aquatic organisms is low but the chronic risk to fish and daphnids is high from the representative uses. Risk mitigation measures such as buffer zones of 15 m are required.

5.3. RISK TO BEES

The acute oral and contact toxicity of the technical active substance and the lead formulation was tested with bees. The endpoints were compared to an application rate of 180 g a.s./ha (= the sum of two applications of 90 g a.s./ha). The HQ values based on endpoints for the technical a.s were calculated to be 1.8 and 2.1. No calculation for endpoints with the formulation was presented in the DAR. If the lowest endpoints from the study of Schmitzer (1999) (acute contact LD_{50} >100 µg formulation/L = > 6 µg a.s./L and acute oral LD_{50} > 139.7 µg formulation/L = > 8.38) are used, the resulting HQ values are < 30 (= 180/6) and < 21.5 (180/8.38). The HQ values based on formulation endpoints are still below the Annex VI trigger of 50. Consequently the risk to bees is considered to be low for the representative uses.

5.4. RISK TO OTHER ARTHROPOD SPECIES

Valid lab tests (on glass plates) were conducted with *Typhlodromus pyri*, *Coccinella septempunctata* and *Poecilus cupreus* at dose rates of 180 g a.s./ha. Effects of > 30 % were observed for *C. septempunctata* and for *T. pyri*. No effects > 50 % were observed in the valid extended lab studies conducted at dose rates of 2 x 90 g a.s./ha with *Aphidius rhopalosiphi*, *Coccinella septempunctata*, and *Pardosa sp.*. *T. pyri* was exposed to 1 day old residues. No effects > 50 % were observed in the aged residue test indicating a low in-field risk to *T. pyri*. A laboratory test was conducted at dose rates equivalent to two different drift rates in order to address the off-field risk to *T. pyri*. No adverse effects of > 30 % were observed at the tested dose rates of 0.54 g a.s./ha and 1.1 g a.s./ha.

During the Evaluation meeting in September 2004 a Member State announced to have a study available on the off-field risk to *T. pyri*. It was decided in the meeting that the study should be made available to the RMS and that it should be evaluated by the RMS, provided that the study was conducted with the lead formulation. The announced study was not submitted to the RMS. Based on the available data the risk to non-target arthropods is considered to be low.

5.5. RISK TO EARTHWORMS

The acute toxicity to earthworms was tested with the technical active substance and the lead formulation. Sublethal effects were investigated only for the technical a.s.. The acute TER values of 3333 for the technical active substance and 197 for the formulated active substance are clearly above the Annex VI trigger of 10. The long-term TER was calculated to be 6 which is above the Annex VI trigger of 5. Hence the risk to earthworms from the representative uses is considered to be low.

5.6. RISK TO OTHER SOIL NON-TARGET ORGANISMS

Since the field DT_{90} in soil is > 365 days a litterbag study is required. No significant effects were observed in the litterbag study which was presented in the DAR. The litterbag study presented in the DAR was discussed in the experts' meeting. The study had several drawbacks (no plateau PECsoil, mesh size too small, short duration). Therefore the meeting decided to ask for a new litterbag study according to EPFES guidance. A data requirement was set for the applicant to submit the new

litterbag study. The applicant stated in the evaluation meeting of January 2005 that this study is already available and could be submitted upon request. This study was not included in the latest corrigendum of the DAR (September 2005). A final conclusion on the risk to soil non-target macro-organisms cannot be drawn until the new litterbag study is available and evaluated.

5.7. RISK TO SOIL NON-TARGET MICRO-ORGANISMS

The effects of the formulated active substance on soil respiration and nitrification were tested with a loamy sand and a sandy loam soil at dose rates of 0.12 mg a.s./kg dry soil and 1.2 mg a.s./kg dry soil. The dose rates were equivalent to 90 and 900 g a.s./ha. No effects of > 25% were observed at the dose rate of 0.12 mg a.s./kg dry soil. At the 10 fold higher dose rate a maximum effect of 28.9 % was observed on day 14 in the loamy sand. Since this effect was observed at a dose rate which is 8 times higher than the calculated accumulated soil concentration (0.15 mg a.s./kg dry soil) it is concluded that the risk to soil non-target micro-organisms is low if the product is applied according to the GAP.

5.8. RISK TO OTHER NON-TARGET-ORGANISMS (FLORA AND FAUNA)

Two tests with the lead formulation and 6 crop species, sugar beet, (*Beta vulgaris*), lettuce (*Lactuca sativa*), radish (*Raphanus sativus*), soybean (*Glycine max*), onion (*Allium cepa*) and oat (*Avena sativa*) were conducted. No effects were observed on seedling emergence and vegetative vigour at the highest tested dose of 90 g a.s./ha. The RMS concluded that the risk for non-target plants is low. The risk to non-target plants was discussed in the experts' meeting. Concerns were raised because the representative use comprises two applications of 90 g a.s./ha and no multiple application factor was taken into account in the risk assessment. However, since no effects were observed at the dose rate of 90 g a.s./ha it was agreed in the meeting that the risk to non-target organisms is assumed to be low.

5.9. RISK TO BIOLOGICAL METHODS OF SEWAGE TREATMENT

No inhibitory effect on respiration of activated sewage sludge was observed in a test with metconazole technical at a dose of 1000 mg a.s./L. Therefore the risk to biological methods of sewage treatment is considered to be low.

6. Residue definitions

Note the use of the common name 'metconazole' in the residue definitions below means residues of all 4 isomers (2 diastereoisomer pairs) as defined by this ISO common name.

Soil

Definitions for risk assessment: metconazole

Definitions for monitoring: metconazole

Water

Ground water

Definitions for exposure assessment: metconazole

Definitions for monitoring: metconazole

Surface water

Definitions for risk assessment: metconazole and CL 359139[10]

Definitions for monitoring: metconazole

Air

Definitions for risk assessment: metconazole

Definitions for monitoring: metconazole

Food of plant origin

Definitions for risk assessment: metconazole (cereals and oilseed crops only)

Definitions for monitoring: metconazole (cereals and oilseed crops only)

Food of animal origin

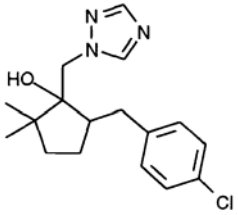
Definitions for risk assessment: metconazole

Definitions for monitoring: metconazole

[10] CL 359139: 3-(4-Chlorobenzyl)-2-hydrooy-1-methyl-2-[1,2,4]triazol-1-ylmethyl-cyclopentane-carboxylic acid

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

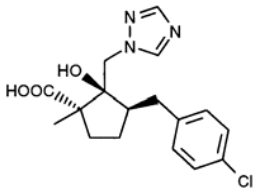
Soil

Compound (name and/or code)	**Persistence**	**Ecotoxicology**
Metconazole 	Medium to highly persistent (single first order DT_{50} lab (20°C, -10kPa) 84-598 days, single first order DT_{50} field 49-259 days)	The acute risk to earthworms is low (TERacute = 3333), the long-term risk to earthworms is low (TERlt = 6)

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**
Metconazole	$K_f$oc 726-1718mL/g low mobility	No for all 9 FOCUS groundwater scenarios	yes	Yes	The acute risk to aquatic organisms is low, but the long term risk to fish and daphnids is high.

Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Metconazole	See point 5.2.
CL 359139 	The metabolite CL 359139 reached a maximum of 9 % of the AR after 152 days. It is not clear from the environmental fate data if the concentration of CL 359139 is decreasing or remains at a level close to 10 % of AR. In order to pose a higher risk to aquatic organisms than the parent, the metabolite would have to be 10 times more toxic than metconazole. This is considered as unlikely since the structure is similar to metconazole and the only difference is the formation of a carboxylic acid group. The carboxylic acid group would make it more water soluble and easier for organisms to excrete. Therefore the risk from the metabolite CL 359139 is expected to be lower compared to metconazole.

Air

Compound (name and/or code)	Toxicology
Metconazole	Not acutely toxic after inhalatory exposure; no data available on repeated exposure

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

- Confirmation, from a toxicological and ecotoxicological point of view, is required to verify the new specification (proposed in January 2005) for two impurities (applicant has submitted recently studies to the RMS. The addendum to B.6, December 2005, was neither peer reviewed by other Member States nor discussed in an experts' meeting, data gap identified by RMS and confirmed by the experts' meeting, refer to chapter 1 and 2.8)
- In the case that an MRL for food of animal origin (liver) is set, an analytical method for the determination of metconazole in liver is required (data gap identified by EFSA, date of submission unknown, refer to chapter 1 and 3.2)
- Genotoxicity studies on impurities 3 and 7 (CL354282 and CL 357625) have been performed and presented in an addendum submitted by the RMS in a late stage of the process. Therefore, results were not peer reviewed and are available for assessment at a Member State level.
- According to current guidelines a livestock feeding study with ruminants is triggered and might need to be submitted to provide precise information on quantitative transfer of residues to edible animal matrices. A reassessment of livestock dietary burden and expected residues in animal products, initiated by the EPCO experts' meeting, indicates the occurrence of significant residues (>0.01 mg/kg) in ruminant liver and the need to propose an MRL.(relevant for all uses in cereals, proposed by EFSA, not peer reviewed, submission date unknown; refer to chapter 3.2)
- Additional residue trials (4) in barley and/or oat to complete the data set for the representative uses in Southern Europe (relevant for the uses in barley and oat for S-EU, submission date unknown; refer to chapter 3.1.1)
- Further argumentation/data are required to support the use of yellow hammer (*Emberiza citronella*) and marsh warbler (*Acrocephalus palustris*) as focal species for the refined risk assessment for insectivorous birds and data on more species should be presented to refine the risk (relevant for all representative uses, identified in the EPCO experts' meeting, submission date unknown, refer to point 5.1)
- Further refinement of the long-term risk to herbivorous mammals (relevant for the use in cereals, identified at the EPCO experts' meeting, unknown submission date, refer to point 5.1)
- A refined risk assessment for the risk to birds and mammals from exposure to contaminated drinking water (relevant for all representative uses, proposed by EFSA, not peer reviewed, submission date unknown; refer to chapter 5.1)
- 21-d Daphnid reproduction study under static test conditions (relevant for all representative uses, identified at the EPCO experts' meeting, submission date unknown, refer to point 5.1.)
- A new litterbag study according to EPFES guidance (relevant for all representative uses, data requirement identified at the EPCO experts' meeting, the applicant stated in the evaluation meeting in January 2005 that the study is available and could be submitted upon request, refer to point 5.6)

CONCLUSIONS AND RECOMMENDATIONS

Overall conclusions

The conclusion was reached on the basis of the evaluation of the representative uses as fungicide as proposed by the applicant which comprises broadcast spraying to control foliar and ear diseases in cereals and oilseed rape at application rate up to 90 g metconazole per hectare. Metconazole can be used only as fungicide.

The representative formulated product for the evaluation was "Caramba 60 SL", a soluble concentrate (SL), registered in some EU Member States.

Adequate methods are available to monitor all compounds given in the respective residue definition. Residues in food and soil can be determined with a multi-method (the German S19 method has been validated). For the other matrices only single methods are available to determine residues of metconazole.

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.

The acute oral toxicity of Metconazole is moderate (a classification Xn; R22 is proposed). Metconazole is of low acute dermal and inhalatory toxicity. It is not a skin or eye irritant or a skin sensitiser. The relevant NOAEL for short term toxicity is 4.6 mg/kg bw/day. Overall, Metconazole is not genotoxic or carcinogenic. The NOAEL for chronic toxicity and carcinogenicity is 4.4 mg/kg bw/day. The NOAELs for parental, reproduction and offspring toxicity are 8 mg/kg bw/day; metconazole has shown some evidence of teratogenic potential in rabbits at doses producing no to severe maternal toxicity. Therefore, classification as Repro Cat. 3 (Xn; R63) was agreed during the meeting. The ADI, ARfD and AOEL are 0.01 mg/kg bw/day based on an overall NOAEL of 4 mg/kg bw/d with a safety factor of 400 (increased due to teratogenic effects).Operator exposure is below the AOEL (German model, PPE worn). The exposure during re-entry activities and for bystanders is negligible.

In the plant metabolism studies conducted in wheat and oilseed rape, metconazole, triazolyl alanine and triazolyl acetic acid were identified as the major components of the total residues in the edible plant parts of the tested crops. Triazolyl alanine is a common metabolite of triazole fungicides, and its toxicological profile was considered as sufficiently investigated. The residue of concern in cereals and oilseed crops is therefore metconazole only. The enrichment of edible plant parts of succeeding crops with metconazole was not sufficient to reach quantifiable levels, when metconazole is used according cGAP. A complete residue trials data base on wheat, rye, triticale and oilseed rape was provided for Northern and Southern Europe and allowed MRL proposals. For barley uses in Southern Europe additional trial data need to be submitted to confirm the compliance with currently proposed MRL based on Northern European trials. Due to low consumer exposure industrial or household processing studies are not required.

Since significant residues occur in potential feed stuff, metabolism studies have been submitted in lactating goats and laying hens. In lactating goats, metconazole undergoes an extensive metabolisation, but was still detected in edible goat matrices bar kidney. All the metabolites found in goat tissues have been recovered in the rat. In a non peer reviewed addendum (December 2005) RMS concluded that representative uses do not give rise to significant residues in animal products and MRLs do not need to be proposed. In contrast, estimates of possibly occurring residues levels in animal matrices done by EFSA indicated that relevant residue levels might be expected in ruminant liver. According to current guidelines a feeding study with ruminants would be required and MRLs for food of animal origin (i.e. ruminant liver) need to be proposed.
In laying hens, the metabolic profile was not further investigated and no such data is currently required since the intake by poultry is not significant with regard to the representative uses.
The dietary risk assessment performed for different consumer groups indicates that there are no chronic and acute concerns related to dietary exposure resulting from the representative uses.

Sufficient data were available to satisfy the data requirements and characterise the fate and behaviour of metconazole in the environment as required by the current regulatory framework. However
in natural sediment water systems in terms of accounting for the route of breakdown and completing the material balance of metconazole, we can conclude little more than metconazole is persistent in the sediment of aquatic systems forming low levels of metabolites (there was no evidence that the metabolites formed were mineralised, the only sink identified was unextracted sediment radioactivity). There is therefore greater uncertainty in the aquatic risk assessment presented in this conclusion for metconazole than in assessments that can be carried out for substances that break down more readily and have been demonstrated to ultimately mineralise to CO_2 in natural aquatic systems.

The environmental exposure assessments available are sufficient to complete the necessary EU level estimates of Predicted Environmental Concentrations (PEC) for the representative uses applied for, for annex 1 listing. Because of the persistence of metconazole in soil and aquatic sediment it was necessary for exposure assessments to take into account the potential accumulation of metconazole in these environmental matrices from potential use in consecutive years. Member States must also do this when assessing potential uses of metconazole at the national level. Member States also need to carry out aquatic exposure and risk assessments from the drainage and runoff routes of exposure to surface water, as these routes of entry have not been considered in the EU level assessments completed and peer reviewed.

FOCUS groundwater modelling indicated a low potential for groundwater contamination in vulnerable situations for metconazole above the statutory value of 0.1µg/L, for the uses assessed in this conclusion.

The acute and short-term risk to birds and the acute risk to mammals are low from the representative uses. A high long-term risk was indicated in a first tier risk assessment for insectivorous and

herbivorous birds and herbivorous mammals. The long-term risk to herbivorous birds was sufficiently addressed in a refined risk assessment. Further refinement steps are required to address the risk to small herbivorous mammals for the representative use in cereals. Further information to justify the choice of the focal species and data on more species to refine the long term risk to insectivorous birds is needed for the representative uses in cereals and oilseed rape. The risk of secondary poisoning from uptake of contaminated earthworms is low. The first tier risk assessment from uptake of contaminated drinking water resulted in a high short-term and long term risk to birds and a high long-term risk to mammals. A refined risk assessment for the uptake of contaminated drinking water is required for the intended uses in cereals and oilseed rape.

The acute risk to aquatic organisms is low but the long-term risk to fish and daphnids is high and risk mitigation measures such as buffer zones up to 15 m are required. As some drawbacks have been identified in the litterbag study the experts' meeting set a data requirement to submit a new litter bag study available to the applicant. The evaluation of this new study would allow to complete the risk assessment.
The risk to bees, other non-target arthropods, earthworms, soil non-target micro-organisms and non-target plants is considered to be low for the representative uses.

Particular conditions proposed to be taken into account to manage the risk(s) identified

- In order to reach operator exposure levels below the AOEL, the use of PPE (such as gloves, coveralls and boots) has to be taken into account (refer to point 2.12).
- Risk mitigation measures comparable to non sprayed buffer zones up to 15 m are required to mitigate the risk to aquatic organisms (refer to point 5.2).

Critical areas of concern

- A final specification for the maximum content of certain significant impurities in the technical material cannot be set (refer to chapter 1 and 2.8)
- In the light of the teratogenic effects, an assessment factor of 400 was agreed on, (100 plus an additional factor of 4) in order to obtain a sufficient margin of safety (1000 x) compared to the dose-level were the effect was observed (refer to point 2.10).
- A high long-term risk to insectivorous birds from all representative uses and a high long-term risk to small herbivorous mammals from the representative use in cereals (refer to point 5.1).
- A high long-term risk to aquatic organisms. Risk mitigation measures such as buffer zones of up to 15 m are required (refer to point 5.2).

APPENDIX 1 – LIST OF ENDPOINTS FOR THE ACTIVE SUBSTANCE AND THE REPRESENTATIVE FORMULATION

(Abbreviations used in this list are explained in appendix 2)

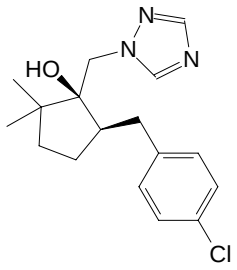
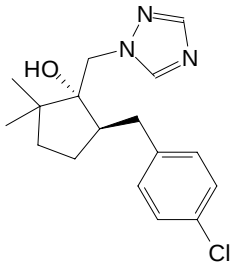
Appendix 1.1: Identity, Physical and Chemical Properties, Details of Uses, Further Information

Active substance (ISO Common Name) ‡	Metconazole
Function (e.g. fungicide)	Fungicide
Rapporteur Member State	Belgium
Co-rapporteur Member State	--

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	*(1RS,5RS:1RS,5SR)*-5-(4-chlorobenzyl)-2,2-dimethyl-1-(1H-1,2,4-triazol-1-ylmethyl) cyclopentanol
Chemical name (CA) ‡	5-[(4-chlorophenyl)methyl]-2,2-dimethyl-1-(1H-1,2,4-triazol-1-ylmethyl) cyclopentanol
CIPAC No ‡	706
CAS No ‡	125116-23-6 (unstated stereochemistry)
EEC No (EINECS or ELINCS) ‡	Not assigned
FAO Specification ‡ (including year of publication)	Not available
Minimum purity of the active substance as manufactured ‡ (g/kg)	Min. 940 g/kg (sum of *cis*- and *trans*-isomers), with *cis*-metconazole (CL 354801) level not less than 800 g/kg and not more than 950 g/kg
Identity of relevant impurities (of toxicological, environmental and/or other significance) in the active substance as manufactured (g/kg)	No impurities are considered to be of toxicological, ecotoxicological or environmental concern
Molecular formula ‡	$C_{17}H_{22}ClN_3O$
Molecular mass ‡	319.8 g/mol

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Structural formula ‡	 cis-isomer CL 354801  trans-isomer CL 354802 The active ingredient of Metconazole is a mixture of 4 diastereomers: CL 354801 ("*cis*-metconazole") is a mixture of *S*(OH), *R* and *R*(OH), *S* diastereomers, whereas CL 354802 ("*trans*-metconazole") is a mixture of *S*(OH), *S* and *R*(OH), *R* diastereomers.

Physical-chemical properties (Annex IIA, point 2)

Melting point (state purity) ‡	Melting point range: 100.0 – 108.4 °C (98.6%)
Boiling point (state purity) ‡	315 °C (98.1%)
Temperature of decomposition	Not applicable (melting and boiling point were determined)
Appearance (state purity) ‡	White powdered solid, odourless (98.6%)
Relative density (state purity) ‡	D_4^{20} = 1.14 (98.6%)
Surface tension	64.8 mN/m at 20 °C (90% saturated solution)
Vapour pressure (in Pa, state temperature) ‡	2.1 x 10^{-8} Pa at 20 °C
Henry's law constant (Pa m^3 mol^{-1}) ‡	2.21 x 10^{-7} Pa.m^3.mol^{-1} at 20 °C
Solubility in water ‡ (g/L or mg/L, state temperature)	30.4 mg/L at 20 °C in distilled Milli-Q water (pH ca. 7.5) (98.6%) no effect of pH
Solubility in organic solvents ‡ (in g/L or mg/L, state temperature)	Solubility at 20 °C in hexane : 1.40 g/L toluene : 103 g/L dichloromethane : 481 g/L methanol : 403 g/L 2-propanol : 132 g/L acetone : 363 g/L ethyl acetate : 260 g/L

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Partition co-efficient (log POW) ‡ (state pH and temperature)	3.85 at 20 °C (pH 7.2 - 8) (98.6%) Effect of pH was not investigated since there is no dissociation in water in the environmentally relevant pH-range
Hydrolytic stability (DT50) ‡ (state pH and temperature)	pH 4 : stable at 50 °C pH 7 : stable at 50 °C pH 9 : stable at 50 °C
Dissociation constant ‡	pKa_1 = 11.38 pKa_2 = 1.08
UV/VIS absorption (max.) ‡ (if absorption > 290 nm state ε at wavelength)	Acetonitrile solution : λ_{max} (nm) — ε ($L.mol^{-1}.cm^{-1}$) 196 — 17700 221 — 5900 226 (shoulder) — 4600 262 — 150 268 — 190 measurement of pH dependency is not necessary (pKa values are outside of the environmentally relevant pH-range) at λ > 290 nm : 2 maxima (determined in pH 7 buffer containing 0.1% acetonitrile) : at 310 nm : ε-value = 2686 $L.mol^{-1}.cm^{-1}$ at 372.5 nm : ε-value = 1921 $L.mol^{-1}.cm^{-1}$
Photostability (DT50) ‡ (aqueous, sunlight, state pH)	Xenon light, 25 °C : pH 5 : 27.5 d pH 7 : 36.3 d pH 9 : 35.8 d
Quantum yield of direct phototransformation in water at Σ > 290 nm ‡	2.19×10^{-7}
Flammability ‡	Not highly flammable
Explosive properties ‡	Not explosive

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

List of representative uses evaluated*

Crop and/or situation (a)	Member State or Country	Formulation name	F, G or I (b)	Pests or Group of pest controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (k)	Remarks (l)
					Type (d-f)	Conc. Of a.s. (i)	Method kind (f-g)	Growth stage (j)	Number min max	Interval between applications; minimum	kg a.s./hl min max	water l/ha min max	kg a.s./ha		
Winter/ spring wheat	North and South Europe	Caramba 60 SL	F	*Septoria spp.* *Septoria nodorum* *Septoria tritici* *Erysiphe graminis* *Puccinia striiformis* *Puccinia recondita* *Fusarium spp.* *Fusarium roseum* *Cladosporium spp.*	SL	60 g/L	spray	BBCH 29-69	1-2	14	0.0225-0.045	200-400	0.090	35	[1]
Winter/ spring barley	North and South Europe	Caramba 60 SL	F	*Erysiphe graminis* *Puccinia hordei* *Rhynchosporium secalis* *Pyrenophora teres*	SL	60 g/L	spray	BBCH 29-69	1-2	14	0.0225-0.045	200-400	0.090	35	[1]

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Crop and/or situation (a)	Member State or Country	Formulation name	F, G or I (b)	Pests or Group of pest controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (k)	Remarks (l)
					Type (d-f)	Conc. Of a.s. (i)	Method kind (f-g)	Growth stage (j)	Number min max	Interval between applications; minimum	kg a.s./hl min max	water l/ha min max	kg a.s./ha		
Winter/ spring oats	North and South Europe	Caramba 60 SL	F	*Puccinia avenae*	SL	60 g/L	spray	BBCH 29-69	1-2	14	0.0225-0.045	200-400	0.090	35	[1]
Rye	North and South Europe	Caramba 60 SL	F	*Erysiphe graminis* *Rhynchosporium secalis* *Puccinia recondita*	SL	60 g/L	spray	BBCH 29-69	1-2	14	0.0225-0.045	200-400	0.090	35	[1]
Triticale	North and South Europe	Caramba 60 SL	F	*Septoria spp.* *Puccinia recondita*	SL	60 g/L	spray	BBCH 29-69	1-2	14	0.0225-0.045	200-400	0.090	35	[1]

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1 – list of endpoints

Crop and/or situation (a)	Member State or Country	Formulation name	F, G or I (b)	Pests or Group of pest controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (k)	Remarks (l)
					Type (d-f)	Conc. Of a.s. (i)	Method kind (f-g)	Growth stage (j)	Number min max	Interval between applications; minimum	kg a.s./hl min max	water l/ha min max	kg a.s./ha		
Oilseed rape	North and South Europe	Caramba 60 SL	F	Phoma *lingam* *Alternaria spp.* *Alternaria brassicae* *Sclerotinia sclerotiorum* *Erysiphe graminis* *Cylindrosporium spp.*	SL	60 g/L	spray	BBCH 14-73	1-2	14	0.0225-0.045	200-400	0.090	56	[1]

[1] The risk assessment has revealed a risk in section 5.

Remarks:				
	*	uses for which the risk assessment can not be concluded are marked grey	(h)	Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated
	(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)	(i)	g/kg or g/L
	(b)	Outdoor or field use (F), glasshouse application (G) or indoor application (I)	(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
	(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	(k)	The minimum and maximum number of application possible under practical conditions of use must be provided
	(f)	Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench		
	(g)	All abbreviations used must be explained	(l)	PHI - minimum pre-harvest interval
			(m)	Remarks may include: Extent of use/economic importance/restrictions

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.2: Methods of Analysis

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

Technical as (principle of method)	HRGC-FID
Impurities in technical as (principle of method)	HRGC-FID
Plant protection product (principle of method)	HPLC-UV

Analytical methods for residues (Annex IIA, point 4.2)

Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	Enforcement method DFG-S19 : GC-NPD (Metconazole, as sum of *cis*- and *trans*-isomer); LOQ = 0.01 mg/kg for each isomer (wheat grain, grapes, pea, oilseed rape seed)
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	*A method has to be required, if the proposed MRL for liver is confirmed.* Multi-residue method DFG-S19: GC-NPD (Metconazole, as sum of *cis*- and *trans*-isomer); LOQ = 0.01 mg/kg for each isomer (milk, meat, eggs, fat)
Soil (principle of method and LOQ)	Enforcement methods FAMS 055-02 and DFG S19: GC-NPD (Metconazole, as sum of *cis*- and *trans*-isomer); LOQ = 0.01 mg/kg for each isomer
Water (principle of method and LOQ)	Enforcement method FAMS 058-01 : GC-NPD (Metconazole, as sum of *cis*- and *trans*-isomer); LOQ = 0.05 µg/L for each isomer (drinking water, surface water)
Air (principle of method and LOQ)	Enforcement method FAMS 067-01 : GC-NPD (Metconazole, as sum of *cis*- and *trans*-isomer); LOQ = 0.28 µg/m^3 for each isomer
Body fluids and tissues (principle of method and LOQ)	Not required (metconazole is not classified as toxic or very toxic)

Classification and proposed labelling (Annex IIA, point 10)

with regard to physical/chemical data	None

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.3: Impact on Human and Animal Health

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

Rate and extent of absorption ‡	Oral: rapid (48h) and efficient (95-97%)
Distribution ‡	Widely distributed up to 72h, tendency for retention in adrenales, GIT, and liver
Potential for accumulation ‡	No evidence
Rate and extent of excretion ‡	Rapid, (67-80% within 48h) for the low dose; slower for the repeated dosing (65-82% within 96h) or for the high dose (67% within 96h) mainly in the faeces, following biliary excretion
Metabolism in animals ‡	Extensive metabolisation, mainly by hydroxylation of cyclopentane- or benzyl ring
Toxicologically significant compounds ‡ (animals, plants and environment)	Metconazole

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral	595 mg/kg bw	**R22**
Mouse LD_{50}, oral	410 mg/kg bw	
Rabbit LD_{50} dermal	>2000 mg/kg bw	
Rat LC_{50} inhalation	>5.6 mg/L air	
Skin irritation	not irritant	
Eye irritation	not irritant	
Skin sensitisation (test method used and result)	not sensitizing	

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect ‡	Liver toxicity (mouse, rat, dog)
Lowest relevant oral NOAEL / NOEL ‡	6.4mg/kg bw/d (90d rat: hepatocellular vacuolation)
Lowest relevant dermal NOAEL / NOEL ‡	Not determined
Lowest relevant inhalation NOAEL / NOEL ‡	Not determined

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Genotoxicity ‡ (Annex IIA, point 5.4)

.....	*In-vitro*: positive in CHO (cis/trans): clastogenic with S9 at 24h but not at 48h sampling time, neither without S9 *In-vivo*: negative in mouse bone marrow and liver UDS

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

Target/critical effect ‡	Liver toxicity (hepatocellular vacuolation/ in mouse and rat; liver hypertrophy/necrosis, ALT/AST increase in mouse); spleen atrophy in mouse; reduced cholesterol/triglyceride levels (mouse); adrenal corticomedullary pigmentation (mouse)
Lowest relevant NOAEL / NOEL ‡	4.3 mg/kg b.w./d (rat)
Carcinogenicity ‡	Mouse: liver cell adenoma/carcinoma; Phenobarbital-like mechanism (enzymatic induction, subsequent to hepatocellular necrosis and cell renewal) rat: not carcinogenic

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction target / critical effect ‡	2G rat (cis): ↓bw gain (F_1 pups), ↑gestation length, ↓ post-implantation survival (F_2)
Lowest relevant reproductive NOAEL / NOEL ‡	Pup toxicity: 8 mg/kg bw/d (↓bw gain Reproduction: 8 mg/kg bw/d (↑gestation length, ↓ post-implantation survival in F2)
Developmental target / critical effect ‡	Increase in post-implantation loss, decrease in foetal size and litter weight , increase in placental weight
Lowest relevant developmental NOAEL / NOEL ‡	NOAEL maternal: 24 mg/kg bw/d (↓feed consumption, ↓bw gain) NOAEL foetal: 24 mg/kg bw/d (↑embryonic deaths, ↑post-implantation loss) NOAEL development: 6 mg/kg bw/d (increased incidence of bilateral hydroureter) **R63**

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

.....	No data, not necessary

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Other toxicological studies ‡ (Annex IIA, point 5.8)

Investigation on enzyme induction	Enzymatic induction in the liver (rat, mouse)
Investigation on in-vitro growth and developmental potential of rat embryos	Inhibition of embryonal growth; induction of various abnormalities by cis/trans and cis Metconazole

Medical data ‡ (Annex IIA, point 5.9)

.....	From existing data (clinical cases, medical surveillance), no adverse effects are expected.

Summary (Annex IIA, point 5.10)	Value	Study	Safety factor
ADI ‡	0.01 mg/kg bw/d	developmental rabbit	400*
AOEL ‡	0.01 mg/kg bw/d	developmental rabbit	400
ARfD ‡ (acute reference dose)	0.01 mg/kg bw/d	developmental rabbit	400

*100 plus an extra SF of 4 due to the teratogenic potential of the a.s.

Dermal absorption (Annex IIIA, point 7.3)

Caramba 60 SL	4% for the concentrate, 65% for the dilution *(In-vitro* rat/human skin absorption study)

Acceptable exposure scenarios (including method of calculation)

Operator	Exposure below the AOEL (25%) when PPE is worn (German model, gloves, coverall and boots)
Workers	Exposure below the AOEL (2.44%)
Bystanders	Exposure below the AOEL (<1%)

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Classification and proposed labelling (Annex IIA, point 10)

with regard to toxicological data	Xn; Harmful R22 Harmful if swallowed R63 Possible risk of harm to the unborn child

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.4: Residues

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

Plant groups covered	Wheat (C), oilseed rape (P/O)
Rotational crops	Wheat (C), lettuce (L), radish (R/T) Metabolic pathway of metconazole in succeeding crops is similar to that in the target crops
Plant residue definition for monitoring	metconazole
Plant residue definition for risk assessment	metconazole
Conversion factor (monitoring to risk assessment)	none

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

Animals covered	Goats, hens
Animal residue definition for monitoring	metconazole
Animal residue definition for risk assessment	metconazole
Conversion factor (monitoring to risk assessment)	None
Metabolism in rat and ruminant similar (yes/no)	Yes
Fat soluble residue: (yes/no)	Yes

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

.....	The studies performed in accordance with GAP showed that the enrichment of edible plant parts of leafy vegetables, root vegetables and cereals, installed as succeeding crops, with metconazole is not sufficient to reach quantifiable levels in monitoring.

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

.....	Residues of metconazole expressed as cis- and trans-isomers in cereal green plant, straw and grain, rape seed and rape oil, carrots and lettuce can be considered as stable under frozen storage conditions for a period of 12 months.

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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

RMS estimates (addendum Dec 2005) in mg/kg, not peer reviewed

Intakes by livestock ≥ 0.1 mg/kg diet/day:	Ruminant: Yes*	Poultry: Yes*	Pig: Yes**
Muscle	0.00014 [1)]	0.0002 [1)]	-
Liver	0.007 [2)]	0.0068 [1)]	-
Kidney	0.000088-0.0002 [2)]	0.0038 [1)]	-
Fat	0.00009 [1)]	0.0013 [1)]	-
Milk	0.00012 [1)]		
Eggs		0.00076-0.0012 [1)]	

* The residue levels indicated for the different matrices are the expected residue levels from the livestock metabolism studies considering the calculated dietary burden values both for ruminants and poultry

** A metabolism study in pigs was not required as metabolic pathways in rat and in goat can be considered as similar. For the same reason, a feeding study in pigs is not required. Moreover, intake calculations for pigs indicate that no significant exposure can be expected.

1) Extrapolated total residue

2) Extrapolated metconazole residue

EFSA estimates, metconazole residues [mg/kg] extrapolated from two goat metabolism studies (EFSA addendum Jan 2006), not peer reviewed

Intakes by livestock ≥ 0.1 mg/kg diet/day:	Ruminant: Yes	Poultry: No	Pig: No
Muscle	<0.01	no data, not assessed, not required	no data, not assessed, not required
Liver	0.013-0.019		
Kidney	<0.01		
Fat	<0.01		
Milk	<0.01		
Eggs		no data, not assessed, not required	

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‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Summary of critical residues data (Annex IIA, point 6.3, Annex IIIA, point 8.2)

Crop	Northern or Southern Europe	Trials results relevant to the critical GAP (a)	Recommendation/comments	MRL (mg/kg)	STMR (mg/kg) (b)
Winter wheat	N	Metconazole (sum of isomers) : -grain : <0.002, <0.01, <0.01, <0.01, <0.01, <0.02, <0.02, 0.04 mg/kg -straw : 0.25, 0.44, 0.53, 0.57, 0.64, 0.75, 0.76, 0.87 mg/kg	Rate of application : 85-90 g a.s./ha, 2 applications – BBCH : 32-39; 65-79 , PHI : 35 days.	0.05	0.02
	S	Metconazole (sum of isomers) : -grain : <0.02, <0.02, <0.02, <0.02, <0.02, <0.02, 0.03, 0.05 mg/kg -straw : 0.16, 0.23, 0.23, 0.23, 0.27, 0.30, 0.30, 0.57 mg/kg	Rate of application : 82-95 g a.s./ha, 2 applications – BBCH : 33-39; 65-77, PHI : 35 days		
Winter/ spring barley	N	Metconazole (sum of isomers) : -grain : <0.01, <0.01, <0.01, <0.01, 0.01, 0.01, 0.01, 0.02, 0.03, 0.03, 0.03, 0.03, 0.03, 0.05, 0.05, 0.09, mg/kg -straw : 0.03, 0.13, 0.15, 0.18, 0.22, 0.23, 0.32, 0.37, 0.73, 0.74, 0.82, 0.99, 1.06, 1.33, 1.37,1.61 mg/kg	Rate of application : 89-96 g a.s./ha, 2 applications BBCH 33; 71-75, PHI : 35-37 days.	0.1 Possible extrapolation to oat (for Northern Europe only) according to EU Doc. 7525/VI/95-rev.7 (Table 3)	0.03

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Crop	Northern or Southern Europe	Trials results relevant to the critical GAP (a)	Recommendation/comments	MRL (mg/kg)	STMR (mg/kg) (b)
Winter/ spring barley	S	Metconazole (sum of isomers) : -grain : 0.03, 0.03, 0.04, 0.05 mg/kg -straw : 1.3, 1.4, 1.5, 2.6 mg/kg	The 4 trials submitted were carried out under GLP conditions with the representative formulation metconazole 60 g/L SL applied 2 times (BBCH 51-83) at a target dose rate of 90 g a.s./ha with a PHI of 35 days		
Winter rye	N	Metconazole (sum of isomers) : -grain : <0.01 mg/kg -straw : 0.37 mg/kg	Trial performed in accordance with the critical GAP.	Possible extrapolation from wheat residue database to rye according to EU Doc. 7525/VI/95-rev.7 (Table 3) MRL proposal for rye: 0.05 mg/kg.	0.02
	S	No data			
Triticale	N	Metconazole (sum of isomers) : -grain : <0.01 mg/kg -straw : 0.16 mg/kg	Trial performed in accordance with the critical GAP.	Possible extrapolation from wheat residue database to triticale according to EU Doc. 7525/VI/95-rev.7 (Table 3) MRL proposal for Triticale: 0.05 mg/kg.	0.02
	S	No data			

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Crop	Northern or Southern Europe	Trials results relevant to the critical GAP (a)	Recommendation/comments	MRL (mg/kg)	STMR (mg/kg) (b)
Oilseed rape	N	Metconazole (sum of isomers) : -seed : <0.01, <0.01, <0.01, <0.01, <0.01, 0.04, 0.06, 0.07 mg/kg.	Rate of application : 90 g a.s./ha, 2 applications – BBCH : 63-67; 69-71 , PHI : 56-70 days	0.1	0.025
	S	Metconazole (sum of isomers) : -seed : <0.01, 0.02, 0.02, 0.02, 0.03, 0.04, 0.05, 0.05, 0.11 mg/kg	Rate of application : 79-90 g a.s./ha, 2 applications – BBCH : 65; 69-75, PHI : 56-63 days		

(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

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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

ADI	0.01 mg/kg bw/day
TMDI (European Diet) (% ADI)	WHO European diet: 3.5 % ADI; German diet (4-6 years old girl): 8 % ADI; Pesticides Safety Directorate Consumer Exposure Model: 3.4 %, 5.8 % and 7.2 % of ADI respectively for adults, children and infants from UK. Additional contribution from food of animal origin to all estimates <1%ADI
NEDI (% ADI)	-
Factors included in NEDI	-
ARfD	0.01 mg/kg bw/day
Acute exposure (% ARfD)	15 % of ARfD for children from UK, additional contribution from food of animal origin <1%ARfD

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

Crop/processed crop

Number of studies	Transfer factor	% Transference *
Not required		

* Calculated on the basis of distribution in the different portions, parts or products as determined through balance studies

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

Wheat, rye, triticale	0.05 mg/kg
Barley[+], oat[+]	0.1 mg/kg
Rape seed	0.2 mg/kg
Ruminant liver **	0.05 mg/kg

[+] Note: data base for S-EU not complete

** EFSA proposal, not peer reviewed; provisional MRL accounting for uncertainty when extrapolating from metabolism study; might be revised upon receipt of precise information on quantitative transfer of metconazole residues to edible animal matrices

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.5: Fate and Behaviour in the Environment

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

Mineralization after 100 days ‡	10.30 % after 120 d, [^{14}C-3,5-triazole]-label (n= 1)
Non-extractable residues after 100 days ‡	39.2 % after 120 d, [^{14}C-3,5-triazole]-label (n= 1) 12.5-28.3% after 112 d, [^{14}C-3,5- cyclopentanol]-label (n= 5)
Relevant metabolites - name and/or code, % of applied ‡ (range and maximum)	CL 382389[1] – 4.56 % at 91d (n= 1)

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

Anaerobic degradation ‡	Mineralisation – 0.26 % after 120 d Non-extractable residues 8.58 % after 120 d No major metabolite [^{14}C-3,5-triazole]-label
Soil photolysis ‡	Mineralisation 1 % after 15 d (irradiated samples) Non-extractable residues 9 % after 15 d Unknown metabolite 1 : 5.0 % at 15 d Unknown metabolite 2 : 2.8 % at 15 d Unknown metabolite 3 : 1.0 % at 15 d Unknown metabolite 4 : 3.0 % at 15 d Mineralisation 0 % after 15 d (dark samples) Non-extractable residues 1.0 % after 15 d [^{14}C-3,5-triazole]-label

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

Method of calculation	Laboratory: first order kinetics Field studies: mainly first order , square root first order at 3 sites

[1] (2-Hydroxy-3,3-dimethyl-2-[1,2,4]triazol-1-ylmethyl-cyclopentyl)-(4-chlorophenyl)-methanone

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Laboratory studies ‡ (range or median, with n value, with r^2 value)	parent DT_{50lab} (20°C, aerobic): 84 d, (1^{st} order n= 1, r^2 = 0.94) (22°C, aerobic): 185-598 d, (1^{st} order n= 5, r^2 = 0.797-0.972) longer than 112 days are extrapolated values For FOCUS gw modelling parent DT_{50lab} (20°C, pF2, aerobic, 1^{st} order kinetics): 84-598 d, mean = 220d (n= 6, r^2 = 0.797-0.972) parent DT_{90lab} (20°C, aerobic): 277 d, (n= 1, r^2 = 0.94) (22°C, aerobic):614-1987 d, mean = 986 (n= 5, r^2 = 0.797-0.972) according to DT_{50} quoted above) DT_{50lab} (study at 10°C, aerobic): 564 d (n= 1, r^2 = 0.7240) DT_{50lab} (20°C, anaerobic): >120 d (n= 1, no DT calculation)
	Degradation in the saturated zone ‡: no data submitted and no data required
Field studies ‡ (state location, range or median with n value)	Bare soil, various formulations and application rates May/June applications Northern Europe: UK Germany DT_{50f}: 70-259 d, (n= 5, r^2= 0.70-0.95) 1^{st} order 33-40 d, (n= 3, r^2= 0.85-0.95) square root 1^{st} order Southern Europe France DT_{50f}: 49-154 d, (n= 2,) 1^{st} order Northern Europe: UK Germany DT_{90f}: 238-854 d, (n= 5, r^2= 0.70-0.95) 1^{st} order 363-442 d, (n= 3, r^2= 0.85-0.95) square root 1^{st} order Southern Europe: France DT_{90f}: 168-504 d, (n= 2) 1^{st} order

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Soil accumulation and plateau concentration ‡	UK, cereals, 2 appl. of 90 g a.s./ha/ year to cereal cropped plots in May/June over 6 years - Residues metconazole detected at level either close to or below 0.01 mg a.s./kg soil - Residues metconazole detected at max level of 0.03 mg a.s./kg soil, after incorporation of straw during 3 years Calculated accumulated soil concentrations of metconazole: 2x90g/ha, 60% crop interception single first order DT_{50} 259 days application in successive years, 5cm even incorporation soil density 2.5g/cm^3, plateau accumulated amount after 6 years immediately before an application 0.059mg/kg. Maximum plateau concentration 0.15mg/kg

Soil adsorption/desorption (Annex IIA, point 7.1.2)

K_f /K_{oc} ‡ K_d ‡ pH dependence ‡ (yes / no) (if yes type of dependence)	K_{foc}: parent 726-1718 ml/g (mean 1116, $^1/_n$= 0.666-1.02, mean $^1/_n$ 0.88, 9 soils) No pH dependence

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

Column leaching ‡	Soil thin layer chromatography confirmed the low mobility of the active substance
Aged residues leaching ‡	BBA guideline Aged for : 90 d Precipitation: 200 mm Leachate: 0.54-0.87 % total residues in leachate (only metconazole) 88.17-92.42 % total residues/radioactivity retained in top 6 cm
Lysimeter/ field leaching studies ‡	Not provided - not required

PEC (soil) (Annex IIIA, point 9.1.3)

Method of calculation	DT_{50} (d): *259* days Kinetics: 1st order representative worst case from field studies.

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Application rate	Crop: cereals 60 % plant interception: Number of applications: 2 Interval (d): 14 application : 90 g as/ha

PEC$_{(s)}$ (mg/kg)		Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial		0.048 mg a.s./kg		0.094 mg a.s./kg	
Short term	4h	0.048	0.048	0.094	0.094
	2d	0.048	0.048	0.094	0.094
	4d	0.047	0.048	0.093	0.094
Long term	7d	0.047	0.048	0.092	0.093
	28d	0.045	0.046	0.087	0.091
	50d	0.042	0.045	0.082	0.088
	100d	0.037	0.042	0.072	0.083

Long term PEC soil

Worst case field DT_{50},	maximum concentration just after the last application (mg a.s./kg soil)	mean plateau average (mg a.s./kg soil)	maximum plateau average (mg a.s./kg soil)
259	0.15	0.1	0.15

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)	Hydrolytically stable at pH4, 5, 7, 9: 50°C
Photolytic degradation of active substance and relevant metabolites ‡	Xenon arc light source with UV filter, 25°C DT_{50} 27.5-36.3 test system days at pH 5, 7 and 9 hydroxymetconazole: 14.5 %AR (after 30 d at pH 7)
Readily biodegradable (yes/no)	Not readily biodegradable, 2-5% Theoretical CO_2 evolved in 28 days

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Degradation in water/sediment - DT_{50} water ‡ - DT_{90} water ‡ - DT_{50} whole system ‡ - DT_{90} whole system ‡	Water dissipation rate 1-15 days (1^{st} order, r^2= 0.915-0.932, n= 2) 3-49 days (1^{st} order, r^2= 0.915-0.932, n= 2) 116-814 days (1^{st} order, r^2= 0.922-0.923, n= 2) 384->1000 days (1^{st} order, r^2= 0.922-0.923, n= 2)
Mineralization	0 %AR (at 100 d, n= 2)
Non-extractable residues	18.9-11.8 %AR (at 100 d, n= 2)
Distribution in water / sediment systems (active substance) ‡	Maximum of 51.0-78.4 %AR in sediment after 30-100 days. DT_{50} in sediment similar to the DT_{50} whole system
Distribution in water / sediment systems (metabolites) ‡	Occurrence of metabolite M13 (CL 359139[2]) at max level of 9.0% at day 152, in water phase in one w/s system

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

Method of calculation	First order kinetics, maximum DT_{50} of 15 days (water/sediment study)
Application rate	2 applications of 90 g a.s./ha, with an interval of 14 days, (cereals, oilseed rape)
Main routes of entry	Spray drift at 1 m (2.77% drift), 30 cm water body

$PEC_{(sw)}$ (µg / l)		Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial		0.8 µg a.s./L	0.8 µg a.s./L	1.2 µg a.s./L	1.2 µg a.s./L
Short term	4h	0.8 µg a.s./L	0.8 µg a.s./L	1.1 µg a.s./L	1.2 µg a.s./L
	2d	0.8 µg a.s./L	0.8 µg a.s./L	1.1 µg a.s./L	1.1 µg a.s./L
	4d	0.7µg a.s./L	0.8 µg a.s./L	1.0 µg a.s./L	1.0 µg a.s./L
Long term	7d	0.6 µg a.s./L	0.7µg a.s./L	0.9 µg a.s./L	0.9 µg a.s./L
	14d	0.4 µg a.s./L	0.6 µg a.s./L	0.6 µg a.s./L	0.7 µg a.s./L
	21d	0.3 µg a.s./L	0.5 µg a.s./L	0.5 µg a.s./L	0.5 µg a.s./L
	28d	0.2 µg a.s./L	0.4 µg a.s./L	0.3 µg a.s./L	0.3 µg a.s./L
	42d	0.1 µg a.s./L	0.3 µg a.s./L	0.1 µg a.s./L	0.2 µg a.s./L

[2] 3-(4-Chlorobenzyl)-2-hydrooy-1-methyl-2-[1,2,4]triazol-1-ylmethyl-cyclopentane-carboxylic acid

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

PEC (sediment)

Method of calculation	First order kinetics, maximum DT_{50} = 814 days (water/sediment study) assuming as a worst case 100% partitioning to sediment, 1 cm sediment layer, 1.3 kg/dm^3 sediment density
Application rate	2 applications of 90 g a.s./ha, with an interval of 14 days, (cereals, oilseed rape)
Main routes of entry	Spray drift at 1 m (2.77% drift),

PEC$_{(sed)}$ (µg / kg)	Single application Actual	Single application Time weighted average	Multiple application Actual	Multiple application Time weighted average
Initial	0.019 mg a.s/kg sediment (1 application)	-	0.038 mg a.s/kg sediment (after 2nd application)	-
Long term – accumulation through years	-	-		0.12 mg a.s/kg sediment (plateau average) 0.14 mg a.s/kg sediment (maximum accumulated value)

To complete the risk assessment to sediment dwellers a water concentration derrived from the PEC sediment of 0.14 mg a.s./kg taking into account the water to sediment ratio in the ecotoxicology test with chironomous and incorporating that at 30 days in the sediment water study only 65% partitioning to sediment had occurred is required. The characteristics of the chironomous test system were 1800mL of water and 0.239Kg wet weight of sediment (assuming a wet sediment density of 1.3g/mL for the sediment volume in the test systems of 184mL). This 'pseudo' PECsw that accounts for sediment accumulation from 2 applications a year for use in the risk assessment to sediment dwellers is 0.029mg/L

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

Method of calculation and type of study (*e.g.* modelling, monitoring, lysimeter)	Model used: FOCUS_PELMO version 2.2 Scenarios : Châteaudun, Hamburg, Jokionen, Kremsmünster, Okehampton, Piacenza, Porto, Thiva Crop: winter cereals, spring cereals, winter oilseed rape, summer oilseed rape Mean parent DT_{50lab} 247 d (normalisation to pF2, 20°C with Q10 of 2.2). K_{foc}: parent, mean 1000.6 l/lg, $^1/_n$= 0.94.

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Application rate	Application rate: 90 g a.s./ha. 2 applications at interval of 14 days, early-season applications (1 and 3 week post-emergence) and mid-season applications (May-June depending on specific scenarios)

PEC$_{(gw)}$

Maximum concentration	-
Average annual concentration (Results quoted for modelling with FOCUS gw scenarios, according to FOCUS guidance)	Annual average concentrations in µg a.s./L (80th percentile) according to FOCUS guidance (see table below)

Location	Mid-season applications	Early-season applications
Winter Cereals		
Châteaudun	<0.001	<0.001
Hamburg	0.001	0.002
Jokionen	<0.001	<0.001
Kremsmünster	<0.001	<0.001
Okehampton	0.005	0.006
Piacenza	0.023	0.023
Porto	<0.001	<0.001
Sevilla	<0.001	<0.001
Thiva	<0.001	<0.001
Spring Cereals		
Châteaudun	<0.001	<0.001
Hamburg	<0.001	<0.001
Jokionen	<0.001	<0.001
Kremsmünster	<0.001	<0.001
Okehampton	<0.001	<0.001
Porto	<0.001	<0.001

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Location	Mid-season applications	Early-season applications
Winter Oilseed Rape		
Châteaudun	<0.001	<0.001
Hamburg	0.002	0.002
Jokionen	0.001	0.001
Kremsmünster	0.007	0.008
Okehampton	0.014	0.016
Porto	<0.001	<0.001
Summer Oilseed Rape		
Jokionen	<0.001	<0.001
Okehampton	<0.001	<0.001
Porto	<0.001	<0.001

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

Direct photolysis in air ‡	Not studied - no data requested
Quantum yield of direct phototransformation	ϕ = 2.19 x 10-7
Photochemical oxidative degradation in air ‡	DT_{50} of 6.5 hours derived by the Atkinson method of calculation assuming a 12 h OH radical concentration of 1.5x106 radicles cm-3.
Volatilization ‡	From plant surfaces (BBA guideline): 5 % after 24 hours from soil (BBA guideline): 13-14 % after 24 hours

PEC (air)

Method of calculation	Expert judgement, based on vapour pressure ($2.1 \cdot 10^{-8}$ Pa at 20°C) and information on volatilisation from plants and soil.

$PEC_{(a)}$

Maximum concentration	Negligible

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Definition of the Residue (Annex IIA, point 7.3)

Relevant to the environment	Requiring risk assessment Soil, groundwater water sediment and air: metconazole alone Surface water metconazole and CL 359139 Appropriate for monitoring All compartments metconazole alone

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)	Not available
Ground water (indicate location and type of study)	Not available
Air (indicate location and type of study)	Not available

Classification and proposed labelling (Annex IIA, point 10)

with regard to fate and behaviour data	R53 May cause long-term adverse effects in the aquatic environment

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Appendix 1.6: Effects on non-target Species

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

Acute toxicity to mammals ‡	LD_{50} (mouse) = 410 mg a.s./kg bw
Reproductive toxicity to mammals ‡	NOEC (rabbit, terato) = 4 mg a.s./kg bw/day
Acute toxicity to birds ‡	LD_{50} = 787 mg a.s./kg bw
Dietary toxicity to birds ‡	LC_{50} = 167.85 mg a.s./kg bw/day
Reproductive toxicity to birds ‡	NOEC (22 weeks) = 6.19 mg a.s./kg bw/day

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

First tier risk assessment (birds)

Application rate	Bird type	Time scale	FIR/ bw	RUD (90%)	MAF	f_{twa}	ETE (mg a.s./kg bw/day)	TER	Annex VI trigger value
2 x 0.090 kg a.s./ha in cereals	Large herbi-vorous bird	acute	0.44	142	1.2	-	6.75	116.6	10
		short term	0.44	76	1.4	-	4.21	39.87	10
		long term	0.44	76	1.4	0.53	2.23	2.78	5
	Insecti-vorous bird	acute	1.04	52	-	-	4.87	161.6	10
		short term	1.04	29	-	-	2.71	61.94	10
		long term	1.04	29	-	-	2.71	2.28	5
2 x 0.090 kg a.s./ha in oilseed rape	med. herbi-vorous bird	Acute	0.76	87	1.2	-	7.1	110	10
		short term	0.76	40	1.4	-	3.8	44.4	10
		long term	0.76	40	1.4	0.53	2.03	3.1	5
	Insecti-vorous bird	Acute	1.04	52	-	-	4.87	161.7	10
		short term	1.04	29	-	-	2.71	61.8	10
		long term	1.04	29	-	-	2.71	2.3	5

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Application rate (kg as/ha)	Crop	Category	Time-scale	TER	Annex VI Trigger
2 x 0.09	Cereals	Bird eating earthworms	Long term	6.19/0.59= 10.5	5
		Bird eating fish	Long term	6.19/0.033=189	5

Second tier risk assessment (birds)

Application rate	Bird type	FIR/ bw*)	Category	RUD (mean)	PT	PD	IF	f_{twa}	MAF	ETE (mg a.s./kg bw/day)	TER	Annex VI trigger value
2 x 0.09 kg a.s./ha in cereals	Large herbi-vorous bird (Goose)	0.44	cereal green plant	20.75	1	1	1	0.53	1.0	0.44	**14**	5
	Insecti-vorous bird early (Yellow-hammer)	0.78	Arthropodes (soil surface)	29	0.02	0.65	0.5	-	-	0.013	-	-
		0.78	Arthropodes (in soil)	0	0.02	0.25	0.5	-	-	0.0	-	-
		0.78	weed seeds (soil surface)	40	0.02	0.10	0.5	-	-	0.003	-	-
										0.016	**387**	5
	Insectivorous bird late (Marsh warbler)	0.98	Foliar insects	29	0.027	1	1	-	-	0.07	**88.4**	5

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

First tier risk assessment (mammals)

Application rate	Mammal type	Time scale	FIR/bw	RUD (90%)	MAF	f_{twa}	ETE (mg a.s./kg bw/day)	TER	Annex VI trigger value
2 x 0.090 kg a.s./ha in cereals	Small herbi-vorous mammal	acute	1.39	142	1.2	-	21.32	19.23	10
		long term	1.39	76	1.4	0.53	7.05	0.57	5
	Insecti-vorous mammal	acute	0.63	14	-	-	0.79	519	10
		long term	0.63	5.1	-	-	0.29	13.8	5
2 x 0.090 kg a.s./ha in oilseed rape	med. herbi-vorous mammal	acute	0.28	87	1.2	-	2.63	155.1	10
		long term	0.28	40	1.4	0.53	0.75	5.3	5

Application rate (kg as/ha)	Crop	Category	Time-scale	TER	Annex VI Trigger
2 x 0.09	Cereals	Mammals eating earthworms	Long term	4 /0.75= 5.3	5
		Mammals eating fish	Long term	4/0.02 = 200	5

Second tier risk assessment (mammals)

Application rate	Mammal type	Time scale	FIR/bw	RUD (mean, based on analytical results)	MAF	f_{twa}	ETE (mg a.s./kg bw/day)	TER	Annex VI trigger value
2 x 0.090 kg a.s./ha in cereals	Small herbiv-orous mammal (vole)	acute	1.39	20.75	1	0.53	1.38	2.9	5

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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	Endpoint	Toxicity (mg a.s./L)
Laboratory tests ‡				
Salmo gairdneri	metconazole	72h	mortality	LC_{50} = 2.1
Onchorrhynchus mykiss		28d	mortality	NOEC = 1.14
Onchorhynchus mykiss		95d	survival	NOEC = 0.00291
Daphnia magna		48h	immobilisation	LC_{50} = 4.2
Daphnia magna		21d	reproduction	NOEC = 0.16
Selenastrum capricornutum		72h	biomass	E_bC_{50} = 1.7
Chironomus riparius		28d	emergence	NOEC = 2.12
Onchorhynchus mykiss	metconazole 60 g/L SL	96h	mortality	LC_{50} = 14.83
Daphnia magna		48h	immobilisation	EC_{50} = 0.365
Selenastrum capricornutum		72h	biomass	E_bC_{50} = 5.13
Onchorhynchus mykiss		28 d	mortality	NOEC = 0.242
Daphnia magna		21 d	reproduction	NOEC = 0.0208

Microcosm or mesocosm tests
Not required.

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

Application rate (kg as/ha)	Test substance	Organism	Time-scale	Distance (m)	TER	Annex VI Trigger
2 x 90 g a.s./ha in cereals and oilseed rape	metconazole	*Salmo gairdneri*	Acute	1 m	1750	100
		Onchorhynchus mykiss	Long term	1 m	2.43	10
				5 m	11.78	10
		Daphnia magna	Acute	1 m	3500	100
		Daphnia magna	Long term	1 m	133	10
		S. capricornutum	Acute	1 m	1417	10

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Application rate (kg as/ha)	Test substance	Organism	Time-scale	Distance (m)	TER	Annex VI Trigger
2 x 90 g a.s./ha in cereals and oilseed rape	metconazole	*Chironomus riparius*	Long term	1 m	1767 or 74 when accum. PECsed considered	10
	metconazole 60 g/L SL	*Onchorhynchus mykiss*	Acute	1 m	702.8	100
		Daphnia magna	Acute	1 m	17.3	100
				5 m	84	100
				10 m	165	100
		S. capricornutum	Acute	1 m	243.13	10
		Onchorhynchus mykiss	Long term	1 m	11.47	10
		Daphnia magna	Long term	1 m	0.986	10
				5 m	4.79	10
				10 m	9.4	10
				15 m	13.65	10

Bioconcentration

Bioconcentration factor (BCF) ‡	129
Annex VI Trigger:for the bioconcentration factor	100
Clearance time (CT_{50}) (CT_{90})	< 1 day
Level of residues (%) in organisms after the 14 day depuration phase	0.4%

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

Acute oral toxicity ‡	LD_{50} (72h) = 85 µg a.s./bee
Acute contact toxicity ‡	LD_{50} (96h) > 100 µg a.s./bee

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

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

Application rate (kg as/ha)	Crop	Route	Hazard quotient	Annex VI Trigger
Laboratory tests				
0.18	cereals and oilseed rape	oral	180/100 = 1.8	50
		contact	180/85 = 2.1	50

Field or semi-field tests
Not required.

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

Species	Stage	Test Substance	Dose (kg as/ha)	Endpoint	Effect	Annex VI Trigger
Laboratory tests ‡						
Poecilus cupreus	Adult	Metconazole 60 g a.s./L SL	180 g a.s./ha	Mortality Feeding	E = -4.8%	30%
Coccinella septempunctata	Larvae	Metconazole 60 g a.s./L SL	180 g a.s./ha	Mortality Fecundity	E = 66.45%	30%
Typhlodromus pyri	Protonymphs	Metconazole 60 g a.s./L SL	180 g a.s./ha	Mortality Fecundity	E = 100%	30%
Typhlodromus pyri	Protonymphs	Metconazole 60 g a.s./L SL	1.1 g a.s./ha	Mortality Fecundity	E = 6.85%	30%
Extended lab						
Pardosa	Adult	Metconazole 60 g a.s./L SL	2 x 90 g a.s./ha	Mortality Feeding	E = -0.5%	30%
Coccinella septempunctata	Larvae	Metconazole 60 g a.s./L SL	2 x 90 g a.s./ha	Mortality Fecundity	E = 22.3%	30%
Aphidius rhopalosiphi	Adult	Metconazole 60 g a.s./L SL	2 x 90 g a.s./ha	Mortality Fecundity	E = -45.2%	30%
Typhlodromus pyri	Protonymphs	Metconazole 60 g a.s./L SL	2 x 90 g a.s./ha	Mortality Fecundity	E = 3.4%	30%

Field or semi-field tests
Not required

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Effects on earthworms (Annex IIA, point 8.4, Annex IIIA, point 10.6)

Acute toxicity ‡	LC_{50} > 1000 mg a.s./kg soil (corrected value : 500 mg/kg)
Reproductive toxicity ‡	NOEC = 1.8 mg a.s./kg soil (corrected value : 0.9 mg/kg)

Toxicity/exposure ratios for earthworms (Annex IIIA, point 10.6)

Application rate (kg as/ha)	Crop	Time-scale	TER	Annex VI Trigger
2 x 90 g a.s./ha	cereals and oilseed rape	acute	>500/0.15 = 3333	10
		long term	= 0.9/0.15 = 6	5

Effects on soil micro-organisms (Annex IIA, point 8.5, Annex IIIA, point 10.7)

Nitrogen mineralization ‡	< 25% effect after 28 days at 1.2 mg a.s./kg dry soil (equivalent to 900 g a.s./ha)
Carbon mineralization ‡	< 25% effect after 28 days at 1.2 mg a.s./kg dry soil (equivalent to 900 g a.s./ha)

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

Respiration inhibition	EC_{50} (3h) > 1000 mg/L (nominal)

Effects on other non-target organisms (flora and fauna) believed to be at risk (Annex IIA 8.6; Annex IIIA 10.8)

seedling emergence	NOEC = 0.096 kg a.s./ha for sugar beet (*Beta vulgaris*), lettuce (*Lactuca sativa*), radish (*Raphanus sativus*), soybean (*Glycine max*), onion (*Allium cepa*) and oat (*Avena sativa*)
vegetative vigor	NOEC = 0.08-0.11 kg a.s./ha for sugar beet (*Beta vulgaris*), lettuce (*Lactuca sativa*), radish (*Raphanus sativus*), soybean (*Glycine max*), onion (*Allium cepa*) and oat (*Avena sativa*)

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

Classification and proposed labelling (Annex IIA, point 10)

with regard to ecotoxicological data	Metconazole: N, Harmful to the environment R51/53 Toxic to aquatic organisms, may cause long-term effects on the aquatic environment Caramba: N, Harmful to the environment R50/53 Very toxic to aquatic organisms, may cause long-term effects on the aquatic environment

‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

APPENDIX 2 – ABBREVIATIONS USED IN THE LIST OF ENDPOINTS

ADI	acceptable daily intake
AOEL	acceptable operator exposure level
ARfD	acute reference dose
a.s.	active substance
bw	body weight
°C	degree Celsius (centigrade)
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
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
GC	gas chromatography
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
HRGC	high resolution gas 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
PEC	predicted environmental concentration
PEC_A	predicted environmental concentration in air
PEC_S	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
TLV	threshold limit value
TMDI	theoretical maximum daily intake
TMRC	theoretical maximum residue contribution
TMRL	temporary maximum residue limit
TOC	total organic chlorine
Tremcard	Transport emergency card
tRNA	transfer ribonucleic acid
TSH	thyroid stimulating hormone (thyrotropin)
TWA	time weighted average
UDS	unscheduled DNA synthesis
UF	uncertainty factor (safety factor)

ULV	ultra low volume
UV	ultraviolet
v/v	volume ratio (volume per volume)
WBC	white blood cell
WHO	World Health Organisation
WG	water dispersible granule
wk	week
wt	weight
w/v	weight per volume
w/w	weight per weight
XRFA	X-ray fluorescence analysis
yr	year