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

pyrimethanil

finalised: 13 January 2006

SUMMARY

Pyrimethanil 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.

Austria being the designated rapporteur Member State submitted the DAR on pyrimethanil in accordance with the provisions of Article 8(1) of the amended Regulation (EC) No 451/2000, which was received by the EFSA on 15 April 2004. Following a quality check on the DAR, the peer review was initiated on 18 May 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 8 November 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 and May 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 foliar spraying to control *Botrytis cinerea* in grape (wine), *Venturia inaequalis* in apples and *Botrytis spp.* in protein peas, respectively. The application rates are up to 1 kg pyrimethanil per hectare in grape (wine)[3] and up to 600 g per hectare in apples and protein peas. Pyrimethanil can be used only as fungicide.

[1] OJ No L 53, 29.02.2000, p. 25
[2] OJ No L 224, 21.08.2002, p. 25
[3] It was noted that the application rates per treatment in kg as/hL and water L/ha do not correspond to the application rate per treatment in kg as/ha in the list of representative uses. The notifier is asked to verify these columns. The risk assessment in this conclusion is based on the mentioned application rate.

The representative formulated product for the evaluation was "Scala" ("CQ 1294", "EXP 10588A"), a suspension concentrate (SC), registered in most of the EU Member States.

Adequate methods are available to monitor all compounds given in the respective residue definition. Residues in food of plant origin 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 pyrimethanil.
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.

Pyrimethanil is rapidly orally absorbed (70 – 80 %), and also quickly excreted. There is no potential for bioaccumulation. The metabolic degradation of pyrimethanil in rats occurs primarily via oxidation on one or both rings of the molecule and subsequent conjugation. Pyrimethanil has a low acute toxicity and is not a skin or eye irritant, nor a skin sensitizer. In short term toxicity studies in rats and mice, main target organs were liver (increased weight, histopathological changes) and thyroid (histopathological changes). In dogs, a dose-related marked decrease in water intake was observed. The relevant oral no observed adverse effect level (NOAEL) for short term toxicity is 5.4 mg/kg bw/day (90-days rat study). There is no evidence from the available studies of a mutagenic, genotoxic or carcinogenic potential of pyrimethanil. The relevant oral NOAEL for long term toxicity is 17.3 mg/kg bw/day from the 2-year rat study. Pyrimethanil did not show any adverse effects on reproduction parameters. Pyrimethanil is not teratogenic. No signs of neurotoxicity were observed in any test. Supplementary studies were conducted with the soil metabolite AE F132593. The metabolite was of moderate acute oral toxicity and was found of no genotoxic potential and it can be considered of no toxicological relevance. Mechanistic studies demonstrated that enhanced hepatic metabolism induced by pyrimethanil resulted in an increased thyroid hormone clearance resulting in a chronic stimulation of the thyroid.
The acceptable daily intake (ADI) is 0.17 mg/kg bw/day based on the NOAEL from the 2-year rat study with a safety factor of 100; the acceptable operator exposure level (AOEL) is 0.12 mg/kg bw/day based on the overall NOAEL of 17.4 mg/kg bw/day from the collective results of the 90-day and the 104 week rat study. An additional correction factor was applied due to the limited enteral absorption rate of approx. 72%. From the evaluation of the available toxicological data base of pyrimethanil it was concluded that there is no need to establish an acute reference dos (ARfD).
Based on the results of an *in vitro* study with human skin samples performed with a SC-formulation, a dermal absorption rate of pyrimethanil of 1% for the concentrate and 20% for the spray dilution was proposed for human risk assessment.
According to UK POEM model as well as German BBA model the estimated operator exposure for most of the intended uses is below the AOEL only when appropriate PPE (gloves, coverall) is considered. The estimated worker and bystander exposure is below the AOEL.

The metabolism of pyrimethanil has been investigated in a large range of crops and it was shown that the parent compound is forming the major part of the residue even for PHI as long as 42 days. The metabolites identified do not cause any concern due to their nature and their amount. The residue definition in plant commodities can be limited to pyrimethanil for both monitoring and risk assessment. The supervised residue trials submitted are sufficient to propose the setting of MRLs at 1 and 3 mg/kg for apples and wine grapes respectively. Pyrimethanil is not degraded under processing conditions. The transfer factors to wine, apple juice and puree are below 1, indicating that the compound is preferably transferred to the non food processed fractions. Under field conditions the presence of residues of pyrimethanil and its metabolites in rotational crops is limited to low amounts below 0.05 mg/kg and do not represent a significant toxicological burden.
In cattle pyrimethanil is extensively metabolised and 2 metabolites were identified as major (2-(4-hydroxyanilino)-4,6-dimethylpyrimidine and 2-anilino-4,6-dimethylpyrimidin-5-ol), but their presence at measurable levels under practical condition, taking into account the exposure of livestock through apple pomace and protein peas, can be excluded. Therefore no residue definition for animal commodities is needed.
No dietary risk was identified due to residues resulting from the use of pyrimethanil according to the representative uses in apples, wine grapes and protein peas supported by the manufacturer.

Pyrimethanil is moderate to medium persistent in soil under dark aerobic conditions. The major transformation product was 2-amino-4,6-dimethyl-pyrimidine. This metabolite is moderate to high persistent in soil. Mineralization after 90 -100 d was in the range of 4 - 7 % AR and the bounded residues reached levels between 42 - 62 % AR. The half lives used on the FOCUS ground water modelling were derived from a separated kinetic multicompartmental analysis with TopFit 2.0.
Degradation is much slower under anaerobic conditions (DT_{50} > 300 d).
Dissipation in field trials in Germany confirms that pyrimethanil is a moderate persistent substance in soil ($DT_{50\ field}$ = 23 – 54 d).
PEC soil were calculated for the representative uses based on worst case field half life (DT_{50} = 54 d).
As metabolite 2-amino-4,6-dimethyl-pyrimidine was not detected in field studies the PECmax in soil was estimated from the LOD (LOD ≤ 0.02 mg/kg).
Pyrimethanil is low to high mobile in soil (K_{oc} = 75 – 751 mL / g) and 2-amino-4,6-dimethyl-pyrimidine is medium to high mobile in soil (K_{oc} = 56 – 240 mL / g).
A three years lysimeter study in Germany on two lysimeters with vines is available. No pyrimethanil was found in both lysimeters at any sampling date. Most of the radioactivity in the leachate was found as not extractable from the water phase.
Pyrimethanil is hydrolytically stable in sterile buffer solutions at environmental relevant pH and temperature. Direct photolysis does not contribute to the environmental degradation of pyrimethanil in water. Pyrimethanil is not ready biodegradable.
Degradation of pyrimethanil in dark aerobic water environment at 20 °C was investigated in two water sediment systems. Dissipation of pyrimethanil from the water phase took place with half lives of 8.9 and 24 d, mainly due to adsorption to the sediment. Degradation in the whole system proceeds slowly ($DT_{50\ whole\ system}$ = 40 – 121 d or $DT_{50\ whole\ system}$ = 29 – 114 d with TopFit multicompartmental

kinetic evaluation) with the formation of 2-amino-4,6-dimethyl-pyrimidine (max 10.4 % AR after 100 d in the whole system) and the formation of non extractable sediment residues (max 27.3 – 47.7 % AR). Mineralization was low to moderate (CO_2 = 2.4 – 9.1 % AR).

PEC_{SW} and PEC_{SED} were calculated using the Top Fit derived kinetic constants assuming the application pattern proposed in the table of GAP for the representative uses but only including the spray drift route of entry to surface water. Worst case parameters were selected in the calculation. Peak concentration reached after repeated applications were taken as initial PEC_{SW} / PEC_{SED} for the risk assessment. Member States should assess the potential for soil residues to reach surface water as a result of the drainage and runoff.

Potential for ground water contamination was assessed for pyrimethanil and metabolite 2-amino-4,6-dimethyl-pyrimidine based on FOCUS PELMO 1.1.1. The trigger of 0.1 µg/L was not exceeded for any of the nine scenarios neither by pyrimethanil nor by the metabolite 2-amino-4,6-dimethyl-pyrimidine.

Significant volatilization from leave surface (27 %) and soil surface (10 %) was observed in the study provided. However, the potential for photochemical degradation of pyrimethanil in air is high ($DT_{50\ air\ Atkinson}$ = 1.8 h), indicating very low potential for long transport in air.

The acute and short term risk to birds can be regarded as low for all the representative uses evaluated. Also the long term risk to birds for the representative uses in apples and protein peas and the long term risk to large herbivorous birds in grapes can be regarded as low. The long term risk to insectivorous birds in grapes is high in the first tier risk assessment but based on a weight of evidence approach the EPCO experts' meeting considered the long term risk to insectivorous birds in grapes addressed. The acute risk to mammals is considered to be low but a potential high long term risk to mammals was identified in the first tier risk assessment for all representative uses evaluated. After refinement of these assessments, the long term risk to mammals can be regarded as low for all representative uses evaluated. The EPCO experts' meeting agreed to refine the long term risk to mammals for the use in apples for Annex I inclusion based on the diet composition data for voles as no such data for the most appropriate focal species wood mouse was available. Particular attention should be paid at MS level on the choice of focal species to refine the long term risk to mammals in orchards.

The risk to aquatic organisms is driven by the chronic risk to fish. The EPCO experts' meeting did not accept the available fish ELS study and set a data gap for a new fish ELS study and in addition considered an argumentation for the use of the PEC_{twa}-value necessary. Based on the next most pivotal endpoint the risk to aquatic organisms for the representative use in protein peas and vines can be considered as low without the need for risk mitigation measures. For the representative uses in apple orchards the risk can be regarded as low if risk mitigation measures such as a 10 meter buffer zone are taken into account. The EFSA would like to point out that the risk to aquatic organisms can only be concluded once the new fish ELS study becomes available and that most likely more risk mitigation measures will be needed once this study becomes available.

The risk for bioconcentration in fish from the metabolite AE F132593 cannot be concluded as the LogPow is not known. Therefore the EFSA proposes a data requirement for the notifier to make the LogPow of AE F132593 available.

The risk to bees and non-target arthropods can be regarded as low.

The acute risk to earthworms can be regarded as low. Also the long term risk to earthworms for the uses in protein peas and grapes can be regarded as low but a high long term risk to earthworms from the use in apple orchards was identified. The refinement of this risk was not accepted by the EPCO expert's meeting and therefore the meeting set a further data gap for an additional long term toxicity study to earthworms with the lead formulation Scala with more doses and lower organic material. Furthermore a long term study on earthworms with the soil metabolite 2-amino-4,6-dimethylpyrimidine is requested.

No adverse effects on organic matter breakdown are expected from pyrimethanil from the representative uses evaluated.

The risk to soil non-target micro-organisms from the lead formulation Scala is considered to be low, but a study on soil micro-organisms with the metabolite 2-amino-4,6-dimethylpyrimidine is still required.

The risk from pyrimethanil on non-target plants and biological methods for sewage treatment is considered to be low for all representative uses evaluated.

Key words: pyrimethanil, 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. Pyrimethanil is one of the 52 substances of the second stage covered by the amended Regulation (EC) No 451/2000 designating Austria as rapporteur Member State.

In accordance with the provisions of Article 8(1) of the amended Regulation (EC) No 451/2000, Austria submitted the report of its initial evaluation of the dossier on pyrimethanil, hereafter referred to as the draft assessment report, to the EFSA on 5 April 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 18 May 2004 to the Member States and the main applicant BASF as identified by the rapporteur Member State. Pyrimethanil was originally notified by Aventis Crop Science and subsequently supported by Bayer CropScience before it was sold to BASF.

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 8 November 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 expert meetings organised on behalf of the EFSA by the EPCO-Team at the Federal Office for Consumer Protection and Food Safety in Braunschweig, Germany, in April and 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 10 December 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 8 December 2005)

Given the importance of the draft assessment report including its addendum (compiled version of September 2005 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, B.8) which take into account mostly editorial changes. 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

Pyrimethanil is the ISO common name for *N*-(4,6-dimethylpyrimidin-2-yl)aniline (IUPAC).

Pyrimethanil belongs to the class of anilinopyrimidine fungicides such as cyprodinil and mepanipyrim. It is also classified as pyrimidine fungicides such as cyprodinil and fenarimol. Pyrimethanil rapidly penetrates the cuticle, has translaminar properties and inhibits the secretion of fungal enzymes required for the infection process.

The representative formulated product for the evaluation was "Scala" ("CQ 1294", "EXP 10588A"), a suspension concentrate (SC), registered in most of the EU Member States.

The evaluated representative uses as fungicide as proposed by the applicant which comprises foliar spraying to control *Botrytis cinerea* in grape (wine), *Venturia inaequalis* in apples and *Botrytis spp.* in protein peas, respectively. The application rates are up to 1 kg pyrimethanil per hectare in grape (wine)[4] and up to 600 g per hectare in apples and protein peas. Pyrimethanil can be used only as fungicide.

SPECIFIC CONCLUSIONS OF THE EVALUATION

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

The minimum purity of pyrimethanil as manufactured should not be less than 975 g/kg.
At the moment no FAO specification exists.
It should be noted that the technical material contains one impurity (cyanamide, classified as T, Directive 67/548/EEC) that has to be regarded as relevant. This fact was only identified after the final discussion of the conclusion and therefore not discussed during the peer review process. For this reason, it has not been verified whether or not the proposed maximum limit of 0.5 g/kg cyanamide in the technical material is covered by the available toxicological and ecotoxicological tests. Consequently, this limit should be regarded as provisional.

The content of pyrimethanil in the representative formulation is 400 g/L (pure).

The assessment of the data package revealed no particular area of concern. The main data regarding the identity of pyrimethanil 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 pyrimethanil 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. However, it should be noted that no information is available that demonstrates that the relevant impurity in the technical material is not increasing in the formulation upon storage. Furthermore, no spectra have been provided for cyanamide.

Adequate methods are available to monitor all compounds given in the respective residue definition, i.e. pyrimethanil in food of plant origin, soil, water and air.
In case 2-amino-4,6-dimethylpyrimidine (AE F1312593) will be included in the residue definition for soil, the submitted method should be reconsidered.

[4] It was noted that the application rates per treatment in kg as/hL and water L/ha do not correspond to the application rate per treatment in kg as/ha in the list of representative uses. The notifier is asked to verify these columns. The risk assessment in this conclusion is based on the mentioned application rate.

Residues in food of plant origin 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 pyrimethanil.
The methodology used is GC with MS detection or HPLC with MS/MS detection, respectively.
The need for an analytical method for food of animal origin depends on the final residue assessment (see 3.2, 3.4 and 6). In case no residue definition and/or MRL will be proposed, no analytical method is required. It should be noted that the methods submitted in the dossier for food of animal origin do not fulfil the requirements.

The discussion in the expert meeting (EPCO 25, May 2005) on identity, physical and chemical properties and analytical methods was mainly limited to certain physical and chemical properties of pyrimethanil, analytical methods and some clarification with respect to the formulation.

2. Mammalian toxicology

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

2.1. Absorption, Distribution, Excretion and Metabolism (Toxicokinetics)

Pyrimethanil is rapidly absorbed after oral administration to rats with maximum plasma concentrations for radioactivity evident 0.74 hours (single low dose) and 3.94 hours post dose (single high dose), and also quickly excreted. Approximately >90 % were excreted within the first 24 hours after dosing with most of the dose excreted via urine, the remaining by faeces. Based on the amounts of radioactivity detected in urine, the enteral absorption rate was determined to be in a range of 78.6 – 81.4 % and 71.6 – 72.3 % after single low dose and multiple low dose application, respectively. There was no indication for potential of bioaccumulation of the substance.
Pyrimethanil is extensively metabolised in the rat mainly via oxidation on one or both rings of the molecule to form phenols and subsequent conjugation. No sex difference of the ADME behaviour was observed.

2.2. Acute toxicity

Pyrimethanil is of low acute toxicity in rats by the oral (LD_{50} 4149 mg/kg bw), dermal (LD_{50} > 5000 mg/kg bw) and inhalative route (LC_{50} > 1.98 mg/L; max. attainable concentration). Also in mice low acute oral toxicity was demonstrated (LD_{50} 4665 mg/kg bw). Pyrimethanil is non-irritating to the skin and to the eyes of rabbits and is a non-sensitizer in the Buehler test and in the Magnusson and Kligman maximization study as well, conducted in guinea pigs. No classification for acute toxicity is needed.

2.3. SHORT TERM TOXICITY

Short term toxicity of pyrimethanil was studied in dietary 90-days studies in rats and mice, and in 90-days and 1-year studies in dogs.

In the rat study the main target organs were liver (increase of weight, hypertrophy) and thyroid (follicular epithelial hypertrophy and colloid depletion). In mice, relevant findings concerned the liver (clinical chemistry findings, increased organ weight), thyroid (necrosis of follicular epithelial cells), kidneys (tubular dilatation) and urinary bladder (hyperplasia of the epithelium, uroliths). In dogs relevant findings comprised clinical signs, retardation of body weight gain and some minor effects in haematological and biochemical parameters. In addition, in both dog studies, a dose-related marked decrease in water intake was observed, which was considered an adverse effect.

The relevant NOAEL is 5.4 mg/kg bw/day from the 90-days rat study.

2.4. GENOTOXICITY

Pyrimethanil was tested in a battery of *in vitro* and *in vivo* mutagenicity assays with purity values ranging from 96.4% to 99.4%.

Results from these studies showed that pyrimethanil does not induce base-pair or frame-shift mutation in any of the bacterial tester strains (*S. typhimurium, E.coli*), or gene mutation in mammalian cells in culture (CHO-HRPT assay). No potential for clastogenicity was observed in the *in vitro* metaphase chromosome analysis assay in human lymphocytes or in the *in vivo* mouse micronucleus assay and in the UDS assay in rat hepatocytes with *in vivo* treatment, as well.

In conclusion, there is no evidence from the available studies of a mutagenic or genotoxic potential of pyrimethanil.

2.5. LONG TERM TOXICITY

A combined chronic toxicity/carcinogenicity 2-year study was conducted in rats and an 18-months carcinogenicity study in mice.

In rats liver and thyroid have been identified as the target organs. Liver pathology comprised changes in biochemical parameters, increased organ weight and histological alterations at 5000 ppm. In the thyroid, microscopic examination revealed higher incidences of colloid depletion, hypertrophy of the follicular epithelium, deposition of intracytoplasmic brown pigment and focal hyperplasia of the follicular epithelium also at 5000 ppm. In addition, increased incidences of benign follicular cell tumours of the thyroid gland were evident in males and females at this high dose level. However, statistical significance was not reached.

In mice, there were no treatment-related increases in the incidence of tumours following long-term treatment with pyrimethanil up to 1600 ppm suggestive of a carcinogenic effect. Additionally, there were no treatment-related differences in mortality, clinical signs, body weight or haematological parameters at any dose level. There was an increased incidence in morbidity and mortality in males of all groups, particularly during the first 52 weeks of the study, which was associated with lesions in the urogenital tract. These findings (with no evidence of a clear dose-response relationship) were mostly considered to be caused by male aggression. However, the slightly increased incidence of

urinary bladder distension evident in decedent males at 1600 ppm was suggested to be a possible effect of treatment.

The relevant NOAEL for chronic toxicity/carcinogenicity was set at 17 mg/kg bw/day, from the 2-year study in rat.

2.6. REPRODUCTIVE TOXICITY

In the 2-generation reproduction study in rats, the NOAEL for systemic parental toxicity is 18.4 mg/kg bw/day, based on effects on body weight and body weight gain at the top dose (5000 ppm) at both generations. There were no adverse effects on reproductive parameters of the parental animals at any dose level. However, mean body weight gain of F1 and F2 pups was significantly reduced from day 1 post-partum to weaning at 5000 ppm.

Pyrimethanil was not teratogenic in rats and rabbits after oral administration. In the developmental toxicity study in rats, the NOAEL for maternal and fetal effects was 85 mg/kg bw/d based on reduced maternal body weight gain and food consumption but also clinical signs, decreased mean litter weights and mean fetal body weights at 1000 mg/kg bw/day. Therefore the NOAEL for fetal effects was also set at 85 mg/kg bw/day.

In the developmental study conducted in rabbits, the maternal NOAEL was 45 mg/kg bw/day based clinical signs, reductions in food consumption and initial body weight loss followed by deficits in maternal weight gain at 300 mg/kg bw/day. Foetotoxicity was evident only at 300 mg/kg bw/d by means of decreased mean foetal body weight, increased incidences of skeletal variations and retardation on foetal development. The developmental NOAEL was 45 mg/kg bw/day.

2.7. NEUROTOXICITY

Pyrimethanil does not belong to a chemical family for which testing for (delayed) neurotoxicity is indicated (e.g. organophosphates). In addition, none of the subchronic and chronic toxicity studies conducted with pyrimethanil in rats, mice and dogs demonstrate any effect that would suggest a neurotoxic potential.

2.8. FURTHER STUDIES

Supplementary studies were conducted with the metabolite AE F132593 (*2-amino-4,6-dimethylpyrimidine*) identified as the main metabolite in laboratory soil degradation studies only. The metabolite was of moderate acute oral toxicity in rats (LD_{50} 735 mg/kg bw) and gave no indication of having a mutagenic effect when tested in the bacterial reverse mutation assay. In the EPCO experts' meeting it was agreed that this metabolite is of non-toxicological relevance.

In mechanistic studies, effects of pyrimethanil on hepatic enzymes in rats and mice and, in particular, on the thyroid in rats have been investigated. It was demonstrated that enhanced hepatic metabolism induced by treatment with pyrimethanil produced thyroid hormone imbalance due to increased thyroid hormone clearance resulting in a chronic stimulation of the thyroid.

2.9. MEDICAL DATA

The available data indicate no product-specific health disturbances of plant personnel routinely examined in manufacturing of pyrimethanil. In addition, no clinical cases, incidences of poisoning or adverse work –related health effects in humans have been reported from possible exposure to pyrimethanil.

2.10. ACCEPTABLE DAILY INTAKE (ADI), ACCEPTABLE OPERATOR EXPOSURE LEVEL (AOEL) AND ACUTE REFERENCE DOSE (ARFD)

ADI

Given the results from all relevant studies, the rat can be considered the most sensitive species. The NOAEL from the long term study in the rat is 17 mg/kg bw/day and can be used as relevant on which to set the ADI, therefore. This value is also supported by the parental/developmental NOAEL of 18.4 mg/kg bw/day from the two generation reproduction toxicity study in the rat.

An uncertainty factor of 100 is applied to the NOAEL of 17 mg/kg bw/d, resulting in an ADI of 0.17 mg/kg bw/day.

AOEL

For the definition of the AOEL the overall NOAEL of 17 mg/kg bw/day) can be regarded relevant for setting the AOEL.

Based on this and considering the limited enteral absorption rates (correction for 72% absorption) a systemic AOEL of 0.12 mg/kg bw/day is proposed.

ARfD

Acute oral toxicity studies demonstrate the low acute toxicity of pyrimethanil. No adverse effects were observed early in repeated dose studies at dose levels that were relevant for human exposure. No developmental toxicity was induced by pyrimethanil at dose levels below maternal toxicity. From the evaluation of the available toxicological data base of pyrimethanil it can be concluded that there is no need to establish an ARfD.

2.11. DERMAL ABSORPTION

The dermal absorption of pyrimethanil in a 400 g/L SC-formulation was assessed in an *in-vitro* skin penetration study with human skin samples. For the concentrate, penetration rates were in a range of 0.16% (8 hours exposure) – 0.21% (24 hours exposure). Based on these results a dermal absorption rate of 1% for the concentrate and 20% for the spray dilution can be proposed for human risk assessment.

The dermal penetration value of 20% for the spray dilution obtained from the *in vitro* study is also supported by the results of a calculation based on a mathematical skin permeation model considering physical/chemical parameters of the substance and resulting in a predicted absorption rate of approx. 19% for an aqueous dilution containing 1 mg pyrimethanil/mL.

2.12. EXPOSURE TO OPERATORS, WORKERS AND BYSTANDERS

According to the intended uses by the applicant, the representative formulation SCALA, a SC-formulation containing 400 g pyrimethanil/L should be used as a fungicide in field peas (0.6 kg a.s./ha), grapes (1 kg a.s./ha) and pome fruits (0.6 kg a.s./ha).

Operator exposure:

The operator risk assessments have been conducted according to both the German model[5] and the Predictive Operator Exposure Model (POEM) (UK MAFF; 1992) considering all the intended uses mentioned above.

According to the **POEM model** the results of the exposure estimates for tractor application show that without PPE the proposed systemic AOEL is exceeded for all scenarios. Considering gloves, the systemic exposure is below the proposed AOEL for the scenarios "field peas" and "apples", but is exceeding this value for the scenario "grapes". In case of hand-held equipment in high crops (apples and grapes), the calculated systemic exposure is below the AOEL, when gloves are considered.

Using the **German model** without PPE, the total estimated exposure is below the AOEL for the scenario "tractor application in field crops" (peas), but is exceeding the proposed AOEL for both vehicle mounted application and hand held equipment in high crops (apples and grapes). By wearing of PPE (gloves and standard protective garment) the total exposure can be reduced to values below 0.12 mg/kg bw/d for these scenarios indicating that the recommended use of "SCALA" is acceptable to operators if appropriate PPE is worn.

Estimated exposure as % of systemic AOEL (0.12 mg/kg bw/day)			
Model	Scenario	No PPE	With PPE
UK POEM	Field peas, tractor application (0.6 kg a.s./ha)	473.3 %	75.4 % *
	Grapes, tractor application(1 kg a.s./ha)	179.1 %	121.1 % *
	Apples, tractor application(0.6 kg a.s./ha)	107.5 %	72.5 % *
	Grapes, hand-held application (1 kg a.s./ha)	178.0%	69.8 %*
German BBA	Field peas, tractor application (0.6 kg a.s./ha)	61.9 %	58 % **
	Grapes, tractor application(1 kg a.s./ha)	223.1 %	47.1 %***
	Apples, tractor application(0.6 kg a.s./ha)	133.8 %	28.3 %***
	Grapes, hand-held application (1 kg a.s./ha)	149.1 %	44.0 %***

* gloves during mixing/loading and application

** gloves during mixing/loading

*** gloves during mixing/loading, standard protective garment during application

[5] Uniform Principles for Safeguarding the Health of Applicators of Plant Protection Products [Uniform Principles for Operator Protections]; Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirschaft, Berlin-Dahlem, no. 277

Worker exposure:

"SCALA", a SC-formulation, may be used in field peas, grapes and pome fruits during the growing season. To assess cases where re-entry is necessary (e.g. pruning in grapes and thinning in pome fruits), the worker exposure has been calculated using a model proposed by the German BBA (*Hoernicke et al., 1998*) together with published transfer coefficient data (*EPA Policy Paper, Version 3.1, 2000*).

The estimated worker exposure is below the proposed systemic AOEL (0.12 mg/kg bw/day), even when no re-entry period or PPE for the worker are considered (42.8 % [grapes] and 17.1 % [pome fruits] of AOEL).

Bystander exposure:

On the basis of generic monitoring data (*Lloyd and Cross, 1987*) the level of systemic bystander exposure to pyrimethanil resulting from the use of "SCALA" a SC-formulation in orchards (to be considered the worst case) is equivalent to 18% of the proposed systemic AOEL of 0,12 mg/kg bw/day.

3. Residues

Pyrimethanil was discussed at the EPCO experts' meeting for residues (EPCO 24) in May 2005.

3.1. NATURE AND MAGNITUDE OF RESIDUES IN PLANT

3.1.1. PRIMARY CROPS

The metabolism of pyrimethanil was examined after foliar as well as soil application on carrots representing the crop group 'root vegetables', on tomatoes, apples and grapes, representing the crop group 'fruits' and on lettuce representing the crop group 'leafy vegetables'. Pyrimethanil was shown to be the major part of the total residues present in the edible part of the tested commodities. Metabolites consisting in conjugated forms of hydroxylated pyrimethanil were identified, but always at much lower levels than the parent compound even for PHI as long as 42 days. These metabolites were also present in the rat metabolism and their own toxicity can be therefore considered as covered by the toxicological dossier of the parent compound. As their total amount is low in comparison to that of pyrimethanil, the residue definition for plant commodities can be established as pyrimethanil alone, for monitoring and for risk assessment.

A sufficient number of supervised residue trials were submitted to support MRL proposals according to the representative uses and to allow a robust risk assessment for the safety of the consumer. The HRs (Highest Residues) found in apples, wine grapes and fodder peas are 0.6, 1.98 and 0.3 mg/kg respectively. The respective STMRs (Supervised Trials Median Residues) are 0.22, 0.83 and 0.072 mg/kg. The reliability of these supervised residue trials is supported by storage stability studies on carrots, apples, grapes, tomatoes, dried peas, lettuce and wine indicating that pyrimethanil residues are stable under deep freeze conditions for at least 12 months.

Studies on the effect of processing on the nature and levels of residues present in raw commodities were submitted by the applicant. Under conditions simulating pasteurisation, baking/brewing/boiling

and sterilisation, no degradation of pyrimethanil is observed. The transfer of pyrimethanil residues to processed commodities was investigated in 52 trials for the production of wine and in 4 studies for the production of apple puree and apple juice. The transfer factors from raw commodities to these processed products were below 1, indicating a reduction of the residue levels in wine, apple juice, pomace and puree. In apple press cake, which may be fed to animals, a small concentration of the residues was observed.

3.1.2. SUCCEEDING AND ROTATIONAL CROPS

Two studies were conducted for investigating the possible occurrence of pyrimethanil and its metabolites residues in rotational crops. In a first confined study on bare sandy loam soil, residues of pyrimethanil and of several metabolites were found in wheat, lettuce and radish. In contrast with the metabolism in primary crop, the identified metabolites in rotational crops are present at levels similar to the level of the parent compound. The metabolite generally present at highest levels was C 621 312[6]. The amounts of pyrimethanil and its metabolites found in edible parts of plants sowed or planted 30 days after ageing period were such that residue levels in the range of common analytical limits of quantification could be expected under practical conditions in case of early installation of rotational crops.

Therefore a second study under field condition was carried out. Lettuce was used as first crop and was treated twice with pyrimethanil. In succeeding crops (lettuce, brassica and winter wheat) transplanted or sowed after harvest of lettuce, no residues of pyrimethanil and of its main metabolite identified in the confined study (C 621 312) were present above the limit of quantification used for that study (0.05 mg/kg). This gives indication that the possible presence of residual compounds resulting from the use of pyrimethanil in rotational crops is limited to low amounts and that the resulting toxicological burden can be considered as minor, taking into account the ADI value established for pyrimethanil.

3.2. NATURE AND MAGNITUDE OF RESIDUES IN LIVESTOCK

The metabolism of pyrimethanil has been investigated in lactating cow. No sign of accumulation was observed. Pyrimethanil itself could not be identified in any of the tissues investigated, but the identification of metabolites was not performed in muscle and fat, due to low radioactivity levels <0.01 mg/kg in the individual extracts. One main metabolite was identified in urine, milk and kidneys (SN 614 276[7]). In liver the extractability of residues was low and the extracted material was mainly incorporated in low molecular weight proteins and peptides as well as in RNA and DNA.

The metabolism of pyrimethanil was not investigated in poultry.

Due to the fact that residues were not identified in all bovine matrices and given the absence of a metabolism study in poultry, a proposal for a residue definition is therefore not possible to be made for animal commodities.

[6] C 621 312: 2-anilino-4,6-dihydroxymethyl-pyrimidine
[7] SN 614 276: 2-(4-hydroxyanilino)-4,6-dimethylpyrimidine

Apple pomace and protein peas are feed items that can be produced from crops selected as representative uses of pyrimethanil. Taking into account usual nutrition practices of livestock, the possible highest exposure of animals to residues of pyrimethanil was calculated to be in the range of 0.004, 0.01, 0.007 and 0.006 mg/kg bw/d for dairy cattle, beef cattle, poultry and pigs respectively. A feeding study in dairy cow was carried out at dose levels largely in excess of these expected exposures, demonstrating that residues of pyrimethanil and its metabolites C 614 276 and C 614 277[8] in cattle tissues are not expected under normal conditions. Based on the results of both metabolism and feeding studies, measurable levels of C 614 276 and of C 614 277 can only be present in kidneys and milk at levels of exposure 1 to 2 orders of magnitude above the actual exposure.
A feeding study in poultry was not submitted.

3.3. CONSUMER RISK ASSESSMENT

A chronic dietary risk assessment has been carried out following the Theoretical Maximum Daily Intake (TMDI) calculation model of WHO using the WHO European typical diet for adult consumers (60 kg bodyweight) as well as the national diets of Germany for the 4-6 year old girl (13.5 kg bodyweight) and of UK for high consumers in infants and toddlers populations (97.5th percentile of the distribution). Residues in wine grapes and apples were assumed to be at the level of the respective proposed MRLs. The calculations made for these diets lead to TMDI values far below the ADI of pyrimethanil (3%, 2%, 3% and 6% of the ADI for the European adult consumer, the German 4-6 year old girl, the British school children and infants respectively). It must be noted that TMDI calculations represent a gross overestimation of the actual exposure level.
No short term exposure risk assessment was carried out as no acute reference dose has been established for pyrimethanil.
Therefore no dietary risk was identified due to residues resulting from the use of pyrimethanil according to the representative uses in apples and wine grapes supported by the applicant.

3.4. PROPOSED MRLS

Based on the results of supervised residue trials for representative uses and their analysis according to statistical tools recommended by current guidelines MRLs of 1 and 3 mg/kg can be proposed for apples and wine grapes respectively.
No MRL is proposed for animal commodities, given that data are lacking for establishing a residue definition and that the available information in cattle suggests a no-residue situation.

4. Environmental fate and behaviour

Pyrimethanil was discussed at the EPCO experts' meeting for fate and behaviour in the environment (EPCO 21) in April 2005 in Braunschweig (Germany).

[8] C 614 277: 2-anilino-4,6-dimethylpyrimidin-5-ol

4.1. FATE AND BEHAVIOUR IN SOIL

4.1.1. ROUTE OF DEGRADATION IN SOIL

Pyrimethanil metabolism in soil under dark aerobic conditions at 20 °C was investigated in one study with a loamy sand soil (pH = 6.1, 1.9 % clay, 2.4 % OC) at different application rates and with the substance ^{14}C labelled either at the phenyl or the pyrimidinyl ring of the molecule. This study was performed at exaggerated rates in order to characterize the metabolites formed; therefore the results from this study were completed with the studies presented in the dossier to determine the rate of degradation, performed at more realistic application rates.

A number of minor metabolites were identified resulting from the nitration of the phenyl ring or the oxidation of one of the pyrimidinyl nitrogens. However, the major transformation observed was the break down of the amino bridge to yield the major metabolite **2-amino-4,6-dimethyl-pyrimidine** (SN 512723, ZK 512723, S151, AE F132593; max 51.6 -57.6 % AR after 181-243 d). No information on the mass balance and the amount of unextractable residue and mineralization is reported in this study. In the studies performed to investigate the rate of degradation mineralization after 90 -100 d was in the range of 4 - 7 % AR and the bounded residues reached levels between 42 % to 62 % AR. Metabolite 2-amino-4,6-dimethyl-pyrimidine was formed in lower amounts in the studies where the active substance was applied at more realistic, applications rates. In one degradation study the maximum detected was 8.3 % AR and in the other study, which was part of an aged column leaching study the maximum amount of the metabolite was found to be 11.5 % AR.

Degradation under dark anaerobic conditions at 20 °C was investigated in a study with a sandy loam soil (Speyer 2.2; pH = 6.2, 11.8 % clay, 1.31 % OC). Additional to major metabolite 2-amino-4,6-dimethyl-pyrimidine (max. 13.6 % AR after 30 d) minor metabolite 2-hydroxy-4,6-dimethyl-pyrimidine was also identified under anaerobic conditions. Mineralization was low (max 1.6 % CO_2 after 120 d) and bounded residues amounted up to a maximum of 53.5 % AR after 64 d.

According to the available study, photolysis may contribute to the dissipation of pyrimethanil in soil. However, the low recovery of the irradiated samples (attributed to incomplete combustion of strongly bounded residues) makes the results of this study not quantitatively significant. A broad zone (max. 20.6 % AR) was detected in the radio-HPLC chromatograms as a result of the photolytic degradation of pyrimethanil. This peak was attributed to a number of polar metabolites and no efforts for their characterization are reported.

Dissipation of pyrimethanil under field conditions was investigated in three field studies in a total of eight sites in Germany and a site in France (Maine-et-Loire, Northern EU). In the German trials, Scala 400 SC was applied at a rate of 1.5 Kg a.s. / ha to bare soil. Pyrimethanil residues were found above the LOQ (0.05 mg/kg) in the top 0-10 cm layer. At deeper layers pyrimethanil was generally detected at levels below LOQ with exception of one sample in one of the sites (0.17 mg / kg 3d after application). Major metabolite 2-amino-4,6-dimethyl-pyrimidine was detected in these studies only below the LOQ (0.05 mg /kg). In the French trial a 20 % WP formulation was applied at a rate of 4 x 1 Kg a.s. / ha to vine plants in 20 to 33 d interval. Pyrimethanil residues were found both in the 0-10 cm layer (up to 2.1 mg/kg) and the 0-20 cm layer (up to 0.72 mg/kg). Metabolite 2-amino-4,6-dimethyl-pyrimidine was not analyzed. Due to the drawbacks of the study (lack of weather and soil

data, limited data points) the French trial was only considered to provide additional information by the RMS.

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

Degradation rate of pyrimethanil in soil under aerobic conditions at 20 °C was investigated in the soil employed in the route study and in two additional soils, one with the phenyl labelled substance (pH = 7.8, 21.2 % clay, 3.5 % OC) and the other with the pyrimidinyl labelled one (pH = 6.1, 6.7 % clay, 0.95 % OC). Rate of degradation was also investigated as part of an aged column leaching study with the pyrimidinyl labelled compound in a sandy soil (Speyer 2.1: pH = 5.4, 2.0 % clay, 0.74 % OC). Pyrimethanil is moderate to medium persistent in soil under aerobic laboratory conditions ($DT_{50\ lab\ 20°C}$ = 27 – 82 d). Degradation is much slower under anaerobic conditions (DT_{50} > 300 d).

Rate of degradation of metabolite 2-amino-4,6-dimethyl-pyrimidine under aerobic conditions at 20 °C was investigated in two separated studies in six soils (pH = 6.0-7.6, 5.1-49.5 % clay, 1.51-2.40 % OC). Metabolite 2-amino-4,6-dimethyl-pyrimidine is moderate to high persistent in soil in these conditions ($DT_{50\ lab\ 20°C}$ = 15-146 d).

A separated kinetic analysis with TopFit 2.0 based on a three compartmental model was presented by the applicant and summarized in the DAR by the RMS. The half lives used on the FOCUS ground water modelling were derived from this multicompartmental analysis.

Dissipation in field trials in Germany is slightly faster than the laboratory dark aerobic degradation and confirms that pyrimethanil is a moderate persistent substance in soil ($DT_{50\ field}$ = 23 – 54 d).

PEC in soil were calculated for the representative uses proposed based on worst case field half life (DT_{50} = 54 d). As metabolite 2-amino-4,6-dimethyl-pyrimidine was not detected in field studies the PECmax in soil was estimated from the LOD (LOD ≤ 0.02 mg/kg).

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

Batch adsorption/desorption studies are available for pyrimethanil and its metabolite 2-amino-4,6-dimethyl-pyrimidine. The results for these studies indicate that pyrimethanil is low to high mobile in soil (K_{oc} = 75 – 751 mL / g) and 2-amino-4,6-dimethyl-pyrimidine is medium to high mobile in soil (K_{oc} = 56 – 240 mL / g).

Column (four plus six soils) and aged column (one soil) leaching studies are available for pyrimethanil. Up to 1.5 % AR radioactivity was found in the percolates of the non aged columns, mainly as parent compound. Analysis of the soil segments also show only unchanged parent compound. After the ageing period of 40 d an average 3.6 % AR was recovered from the leachate but not analyzed. In an experiment after 119 d of incubation 0.2 % AR was identified in the leachate as parent pyrimethanil and 0.19 % AR as 2-amino-4,6-dimethyl-pyrimidine.

A three years lysimeter study in Germany on two lysimeters with vines is available. Application rate ranged between 1.3 – 1.7 kg / ha split in three summer applications per season. Product was applied only the first year for lysimeter 1 and the first and second years for lysimeter 2. Samples were taken and analyzed during the three years that lasted the study. No pyrimethanil was found in both

lysimeters at any sampling date. Radioactive residue in the percolate amounted to a maximum of 0.91 µg /L parent equivalents (lysimeter 1, second year). Most of the radioactivity (0.48 µg /L parent equivalents) was found as not extractable from the water phase. EFSA noted that the recovery efficiency of the extraction procedure (C_{18} Bondisil column and n-hexane extraction) had only been demonstrated for the parent compound but not for the main soil metabolite 2-amino-4,6-dimethyl-pyrimidine. Evaluation meeting agreed to set a new data requirement to demonstrate the efficiency of the extraction procedure with respect to the metabolite. The applicant presented a study to address this data requirement on March 2005, short before the experts' meeting. Therefore, it was not possible for the RMS to evaluate the study and it was not discussed in the meeting. After the meeting RMS produced an amended addendum where the results of this study are summarized. This amended addendum has not been peer reviewed. The study shows that recovery of 2-amino-4,6-dimethyl-pyrimidine from the C_{18} Bondisil column is abnormally low (max 64 %). No explanation to this low recovery may be derived from the study. Furthermore, most of the product is only recovered when the column is eluted with acetone and only 4-5 % is recovered with the initial elution with hexane. In the lysimeter study only hexane was used to elute the column preventing any significant elution of the 2-amino-4,6-dimethyl-pyrimidine potentially retained in the column. Nevertheless, RMS founds on the reported loss of radioactivity (0.1 µg /L) an indirect evidence in the lysimeter study to support the assumption of low levels of 2-amino-4,6-dimethyl-pyrimidine in the lysimeter leachates. Whereas the lysimeter may not be considered fully conclusive with respect to the leaching potential of 2-amino-4,6-dimethyl-pyrimidine modelling results indicate that the breaching of the trigger 0.1 µg/L by the use of pyrimethanil according the GAP proposed for the representative uses is very unlikely.

4.2. FATE AND BEHAVIOUR IN WATER

4.2.1. SURFACE WATER AND SEDIMENT

Pyrimethanil is hydrolytically stable in sterile buffer solutions at environmental relevant pH (5, 7, 9) and 22 °C.

Photolysis of pyrimethanil in water was investigated in five different studies. Direct photolysis does not contribute to the environmental degradation of pyrimethanil in water but indirect photolysis due to the presence of photosensitizers may occur. No major photolysis metabolites were identified in any of the studies.

A ready biodegradability study is available. This study shows that pyrimethanil is not ready biodegradable.

Degradation of pyrimethanil in dark aerobic water environment at 20 °C was investigated in a water sediment study with two systems. Dissipation of pyrimethanil from the water phase took place with half lives of 8.9 and 24 d, mainly due to adsorption to the sediment. Degradation in the whole system proceeds slowly ($DT_{50\ whole\ system}$ = 40 – 121 d) with the formation of 2-amino-4,6-dimethyl-pyrimidine (max 10.4 % AR after 100 d in the whole system) and the formation of non extractable sediment residues (max 27.3 – 47.7 % AR). Mineralization was low to moderate (CO_2 = 2.4 – 9.1 % AR).

Top fit program was used to fit the data of the two water sediment system to a six compartment model to simulate adsorption/ desorption of parent and metabolite between the phases and degradation in each of them. The model includes flow from the parent to the sink compartment (non

extractables) in both phases. Whereas the separated degradation rate constants may not be fully reliable in this kind of complex multicompartmental kinetic analysis, it is expected that the set of parameters will describe correctly the system as a whole. According this kinetic evaluation, the overall half lives for pyrimethanil in the whole system (calculated by EFSA from results presented in the DAR) are $DT_{50\ whole\ system}$ = 29 – 114 d.

PEC_{SW} and PEC_{SED} were calculated using the Top Fit derived kinetic constants and with the application pattern proposed in the table of GAP for the representative uses but only including the spray drift route of entry to surface water. Parameters from the system that represent the worst case for each of the compartments (water or sediment) were selected to calculate PECs. Peak concentration reached after repeated applications were taken as initial PEC_{SW} / PEC_{SED} for the risk assessment. Member States should assess the potential for soil residues to reach surface water as a result of the drainage and runoff routes of entry where pertinent at the national level.

No PEC_{SW} or PEC_{SED} were calculated for the metabolite 2-amino-4,6-dimethyl-pyrimidine since it did not exceed the 10 % AR for any of the phases in the water sediment systems. The PEC_{SW} value for TER calculation was based on the worst case assumption that the parent was immediately and completely transformed to 2-amino-4,6-dimethyl-pyrimidine.

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

Potential for ground water contamination was assessed for pyrimethanil and metabolite 2-amino-4,6-dimethyl-pyrimidine based on 80 % percentile average annual concentration at 1m depth resulting from FOCUS PELMO 1.1.1 simulations with the nine FOCUS scenarios. Only use in apples was simulated since it was deemed to represent the worst case application pattern. Input parameters were derived and selected according FOCUS recommended procedure. For the degradation parameters the normalized (temperature and moisture) half lives were derived form the TopFit kinetic analysis presented by the applicant (Pyrimethanil: $DT_{50\ norm}$ = 37 d; 2-amino-4,6-dimethyl-pyrimidine: $DT_{50\ norm}$ = 72 d). The trigger of 0.1 µg/L was not exceeded for any of the nine scenarios neither for pyrimethanil nor for the metabolite 2-amino-4,6-dimethyl-pyrimidine.

4.3. FATE AND BEHAVIOUR IN AIR

Significant volatilization from leave surface (27 %) and soil surface (10 %) was observed in the study provided. However, the potential for photochemical degradation of pyrimethanil in air is high ($DT_{50\ air\ Atkinson}$ = 1.8 h), indicating very low potential for long transport in air.

5. Ecotoxicology

Pyrimethanil was discussed at the EPCO experts' meeting for ecotoxicology (EPCO 22) in April 2005 in Braunschweig (Germany).

5.1. RISK TO TERRESTRIAL VERTEBRATES

The risk to birds and mammals is calculated according to the Guidance Document on Birds and Mammals (SANCO/4145/2000). For the representative use in grapes the risk is calculated for a large herbivorous and an insectivorous bird and for a small herbivorous mammal. For the representative use in apples the risk is calculated for an insectivorous bird and a small herbivorous mammal. For the representative use in protein peas the risk is calculated for a medium herbivorous and an insectivorous bird and for a medium herbivorous mammal.

The acute and short term risk to birds can be regarded as low for all the representative uses evaluated. Also the long term risk to birds for the representative uses in apples and protein peas can be regarded as low. The long term risk to large herbivorous birds in grapes can be regarded as low but the long term risk to insectivorous birds in grapes is high in the first tier risk assessment as the TER of 3.2 is below the Annex VI trigger value. The RMS made a refinement of this risk via a weight of evidence approach available in the addendum of March 2005 which was discussed in the EPCO expert's meeting. The meeting considered the long term risk to insectivorous birds in grapes addressed as the NOAEC was based on the highest concentration tested, the dissipation half-life on insects is expected to be short due to the rapid photodegradation, immigration of untreated insects in the field is expected and PT is assumed to be smaller than one.

The acute risk to mammals is considered to be low for all representative uses evaluated. A potential high long term risk to mammals was identified in the first tier risk assessment for all representative uses evaluated. A refined long term risk assessment was presented in the original DAR. In a first step the risk was refined by considering the residue decline of pyrimethanil on plant material which was agreed in the EPCO expert's meeting. Based on this first refinement step the long term risk to mammals from the use of pyrimethanil in protein peas can be regarded as low. In a second refinement step the NOEL was reconsidered. The next higher NOEL of 45 mg/kg bw from the rabbit teratology study was assumed also not to cause ecologically relevant adverse effects in rats. Based on this refinement step the long term risk to mammals in grapes can be considered as low. The EFSA would like to point out that currently the PPR Panel is drafting an opinion regarding this refinement option in general. Therefore the EFSA would like to propose that the outcome of this opinion is taken into account at MS-level once it becomes available. In a third refinement step the proportion in the diet (PD) was refined. The EPCO experts' meeting considered the wood mouse as the most appropriate focal species to refine the risk. As diet composition of wood mice in orchards is not known, the EPCO experts' meeting agreed to use the bank vole as a focal species and hence the PD of 0.2/0.6/0.2 for short grass/seeds/large insects respectively to refine the risk for Annex I inclusion, since it also covers the risk to wood mouse. Based on this refinement step the long term risk to mammals in orchards can be regarded as low. Particular attention should be paid at MS level on the choice of focal species to refine the long term risk to mammals for the use in apple orchards.
In addition to the long term risk assessment for herbivorous mammals, the RMS calculated the risk for insectivorous mammals. The EPCO experts' meeting did not agree to use an interception factor for the representative uses in grapes and apples to calculate this risk. The meeting considered this as a

non standard scenario for the representative uses evaluated and noted that the first tier risk assessment would lead to a low risk for insectivorous mammals in these crops.

The risk to birds and mammals from secondary poisoning is considered to be low as the logPow is 2.84-3.

In the addendum of March 2005 an argumentation, assuming that plant metabolites are probably not more toxic than the parent considering that hydroxylated forms are more water soluble and rapidly excreted is presented. The EPCO expert's meeting agreed that the risk to birds from exposure to plant metabolites is addressed. A similar argumentation is presented in the original DAR for the risk to mammals from exposure to plant metabolites and hence also the risk to mammals from this exposure route can be regarded as low.

Furthermore an assessment of the risk to birds and mammals from exposure to contaminated drinking water was presented in the addendum of March 2005. The EPCO expert's meeting noted a first tier risk to birds and mammals from this exposure route. The meeting agreed that there is no high concern for this exposure route because the amount of spraying liquid is a big range and for birds the endpoints are set at the highest concentration tested.

5.2. RISK TO AQUATIC ORGANISMS

Algae and *Daphnia magna* are the most sensitive aquatic organisms to pyrimethanil and the lead formulation Scala on an acute time scale. Fish are the most sensitive aquatic organisms to pyrimethanil on a chronic time scale. The risk to aquatic organisms is driven by the chronic risk to fish.

The available fish ELS study was not accepted by the EPCO expert's meeting and the meeting had furthermore a concern for the use of a 91 day PEC_{twa}-value to assess the risk with this study. Therefore the EPCO expert's meeting decided to set a data gap for a new fish ELS study and in addition considered an argumentation (e.g. a discussion of the time to onset of effects) for the use of the PEC_{twa}-value necessary.

The next most pivotal endpoint is the acute EC_{50} for *Daphnia magna*. Based on this acute risk assessment, the risk to aquatic organisms for the representative use in protein peas and vines can be considered as low without the need for risk mitigation measures. For the representative uses in apple orchards the risk can be regarded as low if risk mitigation measures such as a 10 meter buffer zone (TER= 3800/32.53=117) are taken into account. The EFSA would like to point out that the risk to aquatic organisms can only be concluded once the new fish ELS study becomes available and that most likely more risk mitigation measures will be needed once this study becomes available.

Furthermore acute toxicity studies on fish, aquatic invertebrates and algae with the metabolite AE F132593 are available. From these studies it can be concluded that this metabolite is more than one order of magnitude less toxic than the parent. No long term toxicity studies with this metabolite are

considered necessary. The risk to aquatic organisms from the metabolite AE F132593 is considered to be low.

Pyrimethanil is not an herbicide and therefore no studies on aquatic plants are considered necessary.

The risk for bioconcentration in fish is considered to be low as the logPow is below 3 for pyrimethanil. The risk for bioconcentration in fish from the metabolite AE F132593 cannot be concluded as the log Pow is not known. Therefore, the EFSA proposes a data gap to make the log Pow of AE F132593 available.

5.3. RISK TO BEES

Acute contact and oral toxicity studies on bees with pyrimethanil and the lead formulation Scala are available. In addition an inhalation, contact, oral and wetting study with the lead formulation Scala on bees and an acute contact toxicity study with the lead formulation Scala on bumble bees is available. All resulting HQ values do not breach the appropriate Annex VI trigger value indicating a low risk to bees. This is confirmed by a semi-field study during which no effects on foraging bees or hive development were observed at a rate equivalent to 5 L Scala/ha.

5.4. RISK TO OTHER ARTHROPOD SPECIES

In the DAR the in-field application rate to assess the risk to non-target arthropods was calculated based on a MAF of 1 for all representative uses evaluated. The MAF equal to one is based on residue decline studies in which the DT_{50} for pyrimethanil on grape and apple foliage was 2.5 days. The EFSA agrees with setting the MAF to 1 for the use in protein peas but considers a MAF of 1.2 more appropriate for the use in apple orchards (DT_{50} of 2.5 days, minimum spray interval 7 days, 5 applications). According to Escort I and II the in-field application rate for 3-dimensional crops, e.g. orchards and vineyards, can be multiplied by a correction factor of 0.5. Only one application is foreseen for the use in grapes. This leads to an in-field application rate of 0.5 (=1x0.5) kg a.s./ha in grapes, 0.36 (0.6x1.2x0.5) kg a.s./ha in apple orchards and 0.6 kg a.s./ha in protein peas.

A high risk to the indicator species *Aphidius rhopalosiphi* was observed in the laboratory study on glass plates. In an extended laboratory study with *A. rhopalosiphi* no effects on mortality were observed and 9% effect on fecundity at an application rate of 1 kg a.s./ha. Therefore the risk to *A. rhopalosiphi* can be considered as low for the representative uses evaluated.
A mortality of 38% was observed in the laboratory study with the indicator species *Typhlodromus pyri* at an application rate of 1.04 kg a.s./ha.. Therefore the LR_{50} for *T. pyri* is assumed to be > 1.04 kg a.s./ha.. The resulting HQ values are below 1 for all the representative uses evaluated and hence the risk to *T. pyri* can be regarded as low. This is confirmed by a field study in apple orchards during which the lead formulation was applied 5 times at 450 g a.s./ha. During this field study no statistically significant differences in mite densities were observed up to 5 weeks after application.

As effects were seen in the laboratory study on *A. rhopalosiphi*, several additional non target arthropod species were tested. Effects were below 30% at dose rates exceeding the in field dose rates of the representative uses evaluated in the laboratory studies with *Coccygominus turionellae*, *Orius laevigatus*, *Chrysoperla carnea*, *Episyrphus balteatus* and *Poecilus cupreus*. Consequently the risk to these species can be considered as low for the representative uses evaluated.
Effects were above 50% in the laboratory for *Encarsia formosa*, *Trichogramma cacoeciae* and *Coccinella septempunctata*. Effects on parasitic potential of adults were still above 50% in the semi-field study with *E. formosa*. As 0% effect on pupae were observed in the same semi-field study (at 2x 1 kg a.s./day with a 7 day interval) it can be assumed that there is a potential for in-field recovery. Effects were below 50% in a semi-field study with *T. cacoeciae* at 1 kg a.s./ha indicating a low risk to this species for the representative uses evaluated. No significant differences in number of arthropods (*C. septempunctata* and other beneficial insects) were observed in a field study in apple orchards during which the lead formulation was applied at 600 and 1000 g a.s./ha..

No off-field risk assessment is considered necessary as the risk in-field is considered to be low (the in-field recovery for *E. formosa* is based on recovery of the in-field population as the pupae are not affected and not on recolonisation). An off-field risk assessment is presented in the DAR. It is noted by the EFSA that this risk assessment was based on spray drift values for multiple applications which is contradictory with a MAF of 1. It is considered that this would not influence the outcome of the risk assessment in this case and that the risk to non-target arthropods off-field can be considered as low as the off-field HQ values are below 2 for the indicator species *A. rhopalosiphi* and *T. pyri*.

In conclusion the risk to non-target arthropods can be regarded as low which was confirmed by the EPCO expert's meeting. The meeting agreed that enough studies at high enough dose rates are available to address the risk to non target arthropods.

5.5. RISK TO EARTHWORMS

Studies on the acute toxicity to earthworms from pyrimethanil, the lead formulation Scala and the metabolite 2-amino-4,6-dimethylpyrimidine are available. The endpoint for pyrimethanil and the lead formulation Scala were corrected for the organic content of the test soil as the logPow exceeds 2 for pyrimethanil. The corresponding TER-values do not breach the Annex VI trigger value, indicating a low acute risk to earthworms from the representative uses evaluated.

A study on the long term toxicity to earthworms from the lead formulation is available. Also this endpoint was corrected for the organic content of the test soil. The long term risk to earthworms for the representative use in protein peas and grapes can be considered as low as the corresponding TER values do not breach the Annex VI trigger value. The TER-value for the use in apple orchards (TER=3.75) is below the Annex VI trigger value indicating a high long term risk to earthworms for this representative use. A refinement of the assessment is presented in the DAR based on the lower 95%-confidence limit of the EC_{20}-value. This approach was discussed in the EPCO experts' meeting and not accepted as the data set was very limited. Therefore the EPCO expert's meeting decided to set

a data gap for an additional long term toxicity study on earthworms with more doses and lower organic material. The long term risk to earthworms for the representative use in apples can only be concluded once this study becomes available. Furthermore the EPCO experts' meeting discussed the need of a long term toxicity study on earthworms with the metabolite 2-amino-4,6-dimethylpyrimidine. The meeting considered such a study necessary as the metabolite is formed after 105 days and cannot be present during the study with parent. Furthermore long term toxicity to earthworms from the parent was observed.

5.6. RISK TO OTHER SOIL NON-TARGET MACRO-ORGANISMS

A litterbag study with the lead formulation Scala is available to address this annex point. The lead formulation Scala was applied at a rate equivalent to 1.33 mg a.s./kg soil and 4 mg a.s./kg soil. No differences in treated samples and controls were observed at any time point in any sample. It can be concluded from this litter bag study that no adverse effects on organic matter breakdown are expected from pyrimethanil from the representative uses evaluated.

5.7. RISK TO SOIL NON-TARGET MICRO-ORGANISMS

The effects of the lead formulation Scala were tested on soil microbial respiration and nitrogen transformation. No deviations of more than 25 % after 100 days at 10.8 mg a.s./kg soil on soil microbial respiration were observed and no deviations of more than 25 % after 100 days were observed on nitrogen transformation at 1.08 mg as/kg soil (i.e. no breaching of the Annex VI trigger value). The dose rate of 1.08 mg a.s./kg soil is just below the maximum PEC_{soil} of 1.1 mg a.s./kg soil for the representative use in apple orchards. The expected PEC_{soil} concentrations in protein peas and grapes are below 1.08 mg a.s./kg soil. The only effect observed on nitrogen transformation at the end of the study at the higher test concentration of 10.8 mg a.s./kg was an increase of 31.5% of the NO_3-production in one soil at 90 days. The risk to soil non-target micro-organisms from the lead formulation Scala is considered to be low.

The EPCO experts' meeting discussed the need for a study with the soil metabolite 2-amino-4,6-dimethylpyrimidine. This metabolite is a major metabolite and is only formed after 105 days and could therefore not have been present during the studies with the parent. Therefore the EPCO experts' meeting identified a data gap for a study on soil micro-organisms with the metabolite 2-amino-4,6-dimethylpyrimidine.

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

Screening data show that pyrimethanil can be expected to have little impact on insects and mites and that it is unlikely to be phytotoxic under field conditions. In this screening study phytotoxic effects were investigated on 13 species of weed/crop plants were the substance was applied at a rate of 3 kg/ha both pre-emergence and post-emergence. No effects were seen on any plant species and hence the risk from pyrimethanil on non-target plants can be considered as low for the representative uses evaluated.

In another screening study the soil metabolite 2-amino-4,6-dimethylpyrimidine showed no insecticidal, herbicidal or fungicidal effect at concentrations that are predicted from the representative uses evaluated.

5.9. RISK TO BIOLOGICAL METHODS OF SEWAGE TREATMENT

The 3 hour EC_{50} for inhibition of respiration of sewage sludge micro-organisms is 360 mg/L. Based on this study the risk to biological methods of sewage treatment is considered to be low.

6. Residue definitions

Soil

Definitions for risk assessment: pyrimethanil, 2-amino-4,6-dimethyl-pyrimidine-

Definitions for monitoring: pyrimethanil, 2-amino-4,6-dimethyl-pyrimidine (pending assessment of effects on micro-organisms and long term toxicity to earthworms)

Water

Ground water

Definitions for exposure assessment: pyrimethanil, 2-amino-4,6-dimethyl-pyrimidine this metabolite should be cancelled from the residue definition in ground water according to the conclusions in the addendum 2-amino-4,6-dimethyl-pyrimidine

Definitions for monitoring: pyrimethanil

Surface water

Definitions for risk assessment: pyrimethanil

Definitions for monitoring: pyrimethanil

Air

Definitions for risk assessment: pyrimethanil

Definitions for monitoring: pyrimethanil

Food of plant origin

Definitions for risk assessment: pyrimethanil

Definitions for monitoring: pyrimethanil

Food of animal origin

Definitions for risk assessment: not possible to be proposed due to the lack of data; however residues in food of animal origin are expected to be very low

Definitions for monitoring: not possible to be proposed due to the lack of data; however residues in food of animal origin are expected to be very low

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

Soil

Compound (name and/or code)	**Persistence**	**Ecotoxicology**
pyrimethanil	moderate to medium persistent ($DT_{50\ lab\ 20°C}$ = 27 – 82 d)	See 5.5, 5.6 and 5.7
2-amino-4,6-dimethyl-pyrimidine	moderate to high persistent ($DT_{50\ lab\ 20°C}$ = 15-146 d)	No data on toxicity to micro-organisms and long term toxicity to earthworms available.

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 activity**	**Ecotoxicological activity**
pyrimethanil	low to high mobile (K_{oc} = 75 – 751 mL / g)	FOCUS: No trigger exceeded Lysimeter: No trigger exceeded	Yes, but no exposure	Yes	No exposure, assessment not required

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 activity	Ecotoxicological activity
2-amino-4,6-dimethyl-pyrimidine	medium to high mobile (K_{oc} = 56 – 240 mL / g)	FOCUS: No trigger exceeded Lysimeter: No trigger exceeded	No	Not relevant	No exposure, assessment not required

Surface water and sediment

Compound (name and/or code)	Ecotoxicology
pyrimethanil	See 5.2.

Air

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

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

- A shelf-life study to demonstrate that the relevant impurity in the technical material is not increasing in the formulation upon storage (date of submission unknown, data gap identified by EFSA after the final discussion in the evaluation meeting, refer to chapter 1).
- Spectra of the relevant impurity cyanamide (date of submission unknown, data gap identified by EFSA after the final discussion in the evaluation meeting, refer to chapter 1).
- Notifier to submit a new ELS study on fish. An argumentation on the use of a 91 day PEC_{twa}-value to calculate the risk should be given (relevant for all representative uses evaluated; no submission date proposed by the notifier; refer to point 5.2).
- Notifier to submit the log Pow of the metabolite AE F132593 (relevant for all representative uses evaluated; no submission date proposed by the notifier; refer to point 5.2).
- Notifier to submit an additional long term toxicity study to earthworms with the lead formulation Scala with more doses and lower organic material (relevant for the representative use in apple orchards; no submission date proposed by the notifier; refer to point 5.5).
- Notifier to submit long term toxicity study to earthworms with the metabolite 2-amino-4,6-dimethylpyrimidine (relevant for all representative uses evaluated; no submission date proposed by the notifier; refer to point 5.5).
- Notifier to submit a study on soil micro-organisms with the metabolite 2-amino-4,6-dimethylpyrimidine (relevant for all representative uses evaluated; no submission date proposed by the notifier; refer to point 5.7).

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 foliar spraying to control *Botrytis cinerea* in grape (wine), *Venturia inaequalis* in apples and *Botrytis spp.* in protein peas, respectively. The application rates are up to 1 kg pyrimethanil per hectare in grape (wine)[9] and up to 600 g per hectare in apples and protein peas. Pyrimethanil can be used only as fungicide.

The representative formulated product for the evaluation was "Scala" ("CQ 1294", "EXP 10588A"), a suspension concentrate (SC), registered in most of the EU Member States.

Adequate methods are available to monitor all compounds given in the respective residue definition. Residues in food of plant origin 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 pyrimethanil.

[9] It was noted that the application rates per treatment in kg as/hL and water L/ha do not correspond to the application rate per treatment in kg as/ha in the list of representative uses. The notifier is asked to verify these columns. The risk assessment in this conclusion is based on the mentioned application rate.

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.

Pyrimethanil is rapidly orally absorbed (70 – 80 %), and also quickly excreted. There is no potential for bioaccumulation. The metabolic degradation of pyrimethanil in rats occurs primarily via oxidation on one or both rings of the molecule and subsequent conjugation. Pyrimethanil has a low acute toxicity and is not a skin or eye irritant, nor a skin sensitizer. No classification for acute toxicity is needed. The relevant oral NOAEL for short term toxicity is 5.4 mg/kg bw/day (90-days rat study). There is no evidence from the available studies of a mutagenic, genotoxic or carcinogenic potential of pyrimethanil. The relevant oral NOAEL for long term toxicity is 17.3 mg/kg bw/day from the 2-year rat study. Pyrimethanil did not show any reproductive and developmental adverse effects No signs of neurotoxicity were observed in any test.
The ADI is 0.17 mg/kg bw/day and the AOEL is 0.12 mg/kg bw/day. From the evaluation of the available toxicological data base of pyrimethanil it can be concluded that there is no need to establish an ARfD. Dermal absorption of the SC-formulation is 1% for the concentrate and 20% for the spray dilution. According to UK POEM model as well as German BBA model the estimated operator exposure for most of the intended uses is below the AOEL only when appropriate PPE (gloves, coverall) is considered. The estimated worker and bystander exposure is below the AOEL.

The metabolism of pyrimethanil has been investigated in a large range of crops and it was shown that the parent compound is forming the major part of the residue even for PHI as long as 42 days. The metabolites identified do not cause any concern due to their nature and their amount. The residue definition in plant commodities can be limited to pyrimethanil for both monitoring and risk assessment. The supervised residue trials submitted are sufficient to propose the setting of MRLs at 1 and 3 mg/kg for apples and wine grapes respectively. Pyrimethanil is not degraded under processing conditions. The transfer factors to wine, apple juice and puree are below 1, indicating that the compound is preferably transferred to the non food processed fractions. Under field conditions the presence of residues of pyrimethanil and its metabolites in rotational crops is limited to low amounts below 0.05 mg/kg and do not represent a significant toxicological burden.
In cattle pyrimethanil is extensively metabolised and 2 metabolites were identified as major (2-(4-hydroxyanilino)-4,6-dimethylpyrimidine and 2-anilino-4,6-dimethylpyrimidin-5-ol), but their presence at measurable levels under practical condition, taking into account the exposure of livestock through apple pomace and protein peas, can be excluded. Therefore no residue definition for animal commodities is needed.
No dietary risk was identified due to residues resulting from the use of pyrimethanil according to the representative uses in apples, wine grapes and protein peas supported by the manufacturer.

Pyrimethanil is moderate to medium persistent in soil under dark aerobic conditions ($DT_{50\ lab\ 20°C}$ = 27 – 82 d). The major metabolite was 2-amino-4,6-dimethyl-pyrimidine (max. 51.6 - 57.6 % AR after 181-243 d at exaggerated application rate; 8.3 % and 11.5 % AR after 62 and 105 d at lower

application rate). This metabolite is moderate to high persistent in soil in these conditions ($DT_{50\ lab\ 20°C}$ = 15-146 d). Mineralization after 90 -100 d was in the range of 4 - 7 % AR and the bounded residues reached levels between 42 - 62 % AR. A separated kinetic analysis with TopFit 2.0 based on a three compartmental model was presented by the applicant and summarized in the DAR by the RMS. The half lives used on the FOCUS ground water modelling were derived from this multicompartmental analysis.

Degradation is much slower under anaerobic conditions (DT_{50} > 300 d). Under these conditions, major metabolite 2-amino-4,6-dimethyl-pyrimidine (max. 13.6 % AR after 30 d) was found together with minor metabolite 2-hydroxy-4,6-dimethyl-pyrimidine. Mineralization was low (max 1.6 % CO_2 after 120 d) and bounded residues amounted up to a maximum of 53.5 % AR after 64 d.

Photolysis may contribute to the dissipation of pyrimethanil in soil.

Dissipation of pyrimethanil under field conditions was investigated in three field studies in a total of eight sites in Germany and a site in France (Northern EU). Dissipation in field trials in Germany confirms that pyrimethanil is a moderate persistent substance in soil ($DT_{50\ field}$ = 23 – 54 d).

PEC soil were calculated for the representative uses proposed based on worst case field half life (DT_{50} = 54 d). As metabolite 2-amino-4,6-dimethyl-pyrimidine was not detected in field studies the PECmax in soil was estimated from the LOD (LOD ≤ 0.02 mg/kg).

Pyrimethanil is low to high mobile in soil (K_{oc} = 75 – 751 mL / g) and 2-amino-4,6-dimethyl-pyrimidine is medium to high mobile in soil (K_{oc} = 56 – 240 mL / g).

Column (four plus six soils) and aged column (one soil) leaching studies are available for pyrimethanil. A three years lysimeter study in Germany on two lysimeters with vines is available. Most of the radioactivity in the leachate (0.48 µg /L parent equivalents) was found as not extractable from the water phase. No pyrimethanil was found in both lysimeters at any sampling date. An additional study was presented where the efficiency of the extraction procedure with respect to the metabolite 2-amino-4,6-dimethyl-pyrimidine is investigated. This study was summarized in an addendum by the RMS after the experts' meeting. Recovery of 2-amino-4,6-dimethyl-pyrimidine from the C_{18} Bondisil column is abnormally low (max 64 %). Whereas the lysimeter may not be considered fully conclusive with respect to the leaching potential of 2-amino-4,6-dimethyl-pyrimidine modelling results indicate that the breaching of the trigger 0.1 µg/L by the use of pyrimethanil according the GAP proposed for the representative uses is very unlikely.

Pyrimethanil is hydrolytically stable in sterile buffer solutions at environmental relevant pH (5, 7, 9) and 22 °C. Direct photolysis does not contribute to the environmental degradation of pyrimethanil in water but indirect photolysis due to the presence of photosensitizers may occur.

Pyrimethanil is not ready biodegradable.

Degradation of pyrimethanil in dark aerobic water environment at 20 °C was investigated in a water sediment study with two systems. Dissipation of pyrimethanil from the water phase took place with half lives of 8.9 and 24 d, mainly due to adsorption to the sediment. Degradation in the whole system proceeds slowly ($DT_{50\ whole\ system}$ = 40 – 121 d) with the formation of 2-amino-4,6-dimethyl-pyrimidine (max 10.4 % AR after 100 d in the whole system) and the formation of non extractable sediment residues (max 27.3 – 47.7 % AR). Mineralization was low to moderate (CO_2 = 2.4 – 9.1 % AR).

Top fit program was used to fit the data of the two water sediment system to a six compartment model to simulate adsorption/ desorption of parent and metabolite between the phases and degradation in each of them. According this kinetic evaluation, the overall half lives for pyrimethanil in the whole system (calculated by EFSA from results presented in the DAR) are $DT_{50\ whole\ system}$ = 29 – 114 d.

PEC sw and PEC sed were calculated using the Top Fit derived kinetic constants assuming the application pattern proposed in the table of GAP for the representative uses uses, but only including the spray drift route of entry to surface water. Parameters from the system that represent the worst case for each of the compartments (water or sediment) were selected in the calculation. Peak concentration reached after repeated applications were taken as initial PEC sw / PEC sed for the risk assessment. Member States should assess the potential for soil residues to reach surface water as a result of the drainage and runoff routes of entry where pertinent at the national level.

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Potential for ground water contamination was assessed for pyrimethanil and metabolite 2-amino-4,6-dimethyl-pyrimidine based on 80 % percentile average annual concentration at 1m depth resulting from FOCUS PELMO 1.1.1 simulations with the nine FOCUS scenarios. Only use in apples was simulated since it was deemed to represent the worst case application pattern. The trigger of 0.1 µg/L was not exceeded for any of the nine scenarios neither by pyrimethanil nor by the metabolite 2-amino-4,6-dimethyl-pyrimidine.

Significant volatilization from leave surface (27 %) and soil surface (10 %) was observed in the study provided. However, the potential for photochemical degradation of pyrimethanil in air is high ($DT_{50\ air\ Atkinson}$ = 1.8 h), indicating very low potential for long transport in air.

The acute and short term risk to birds can be regarded as low for all the representative uses evaluated. Also the long term risk to birds for the representative uses in apples and protein peas and the long term risk to large herbivorous birds in grapes can be regarded as low. The long term risk to insectivorous birds in grapes is high in the first tier risk assessment but based on a weight of evidence approach the EPCO experts' meeting considered the long term risk to insectivorous birds in grapes addressed. The acute risk to mammals is considered to be low but a potential high long term risk to mammals was identified in the first tier risk assessment for all representative uses evaluated. After refinement of these assessments, the long term risk to mammals can be regarded as low for all representative uses evaluated. The EPCO experts' meeting agreed to refine the long term risk to mammals for the use in apples for Annex I inclusion based on the diet composition data for voles as no such data for the most appropriate focal species wood mouse was available. Particular attention should be paid at MS level on the choice of focal species to refine the long term risk to mammals in orchards.

The risk to aquatic organisms is driven by the chronic risk to fish. The EPCO experts' meeting did not accept the available fish ELS study and set a data gap for a new fish ELS study and in addition considered an argumentation (e.g. a discussion of the time to onset of effects) for the use of the PEC_{twa}-value necessary. Based on the next most pivotal endpoint the risk to aquatic organisms for the representative use in protein peas and vines can be considered as low without the need for risk

mitigation measures. For the representative uses in apple orchards the risk can be regarded as low if risk mitigation measures such as a 10 meter buffer zone are taken into account. The EFSA would like to point out that the risk to aquatic organisms can only be concluded once the new fish ELS study becomes available and that most likely more risk mitigation measures will be needed once this study becomes available.

The risk for bioconcentration in fish from the metabolite AE F132593 cannot be concluded as the logPow is not known. Therefore the EFSA proposes a data gap to make the logPow of AE F132593 available.

The risk to bees and non-target arthropods can be regarded as low.

The acute risk to earthworms can be regarded as low. Also the long term risk to earthworms for the uses in protein peas and grapes can be regarded as low but a high long term risk to earthworms from the use in apple orchards was identified. The refinement of this assessment was not accepted by the EPCO expert's meeting and therefore the meeting set a further data gap for an additional long term toxicity study to earthworms with the lead formulation Scala with more doses and lower organic material. Furthermore a long term study on earthworms with the soil metabolite 2-amino-4,6-dimethylpyrimidine is requested.

No adverse effects on organic matter breakdown are expected from pyrimethanil from the representative uses evaluated.

The risk to soil non-target micro-organisms from the lead formulation Scala is considered to be low, but a study on soil micro-organisms with the metabolite 2-amino-4,6-dimethylpyrimidine is still required.

The risk from pyrimethanil on non-target plants and biological methods for sewage treatment is considered to be low for all representative uses evaluated.

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

- The estimated operator exposure for most of the intended uses is below the AOEL only if appropriate PPE is considered (gloves during mixing/loading; coverall during application) (refer to point 2.12).
- The EPCO experts' meeting agreed to refine the long term risk to mammals for the use in apples for Annex I inclusion based on the diet composition data for voles as no such data for the most appropriate focal species wood mouse was available. Particular attention should be paid at MS level on the choice of focal species to refine the long term risk to mammals in orchards (refer to point 5.1).
- Risk mitigation measures, such as a 10 meter buffer zone, are considered necessary to address the risk to aquatic organisms for the representative uses in apple orchards. The EFSA would like to point out that the risk to aquatic organisms can only be concluded once the new fish ELS study becomes available and that most likely more risk mitigation measures will be needed once this study becomes available (refer to point 5.2).

Critical areas of concern

- It was not possible to verify the proposed maximum limit of 0.5 g/kg for cyanamide in the technical material from a toxicological and ecotoxicological point of view. Member States may require further data to address this (refer to chapter 1).
- The risk to aquatic organisms is driven by the chronic risk to fish. The EPCO experts' meeting did not accept the available fish ELS study and set a data gap for a new fish ELS study and in addition considered an argumentation for the use of the PEC_{twa}-value necessary. The EFSA would like to point out that the risk to aquatic organisms can only be concluded once the new fish ELS study becomes available and that most likely more risk mitigation measures than the proposed bufferzone of 10 m in apple orchards (based on the next most pivotal endpoint) will be needed once this study becomes available.
- A high long term risk to earthworms was identified (TER=3.75) for use in apple orchards. The long term risk to earthworms from this use can only be concluded once the requested new long term study on earthworms becomes available.

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

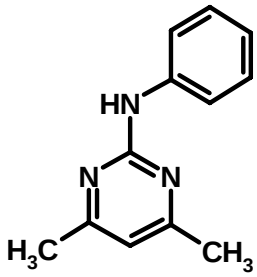
(Abbreviations used in this list are explained in appendix 2)

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

Active substance (ISO Common Name) ‡	Pyrimethanil
Function (e.g. fungicide)	Fungicide

Rapporteur Member State	Austria
Co-rapporteur Member State	--

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	*N*-(4,6-dimethylpyrimidin-2-yl) aniline
Chemical name (CA) ‡	4,6-dimethyl-*N*-phenyl-2-plyrimidinamine
CIPAC No ‡	714
CAS No ‡	53112-28-0
EEC No (EINECS or ELINCS) ‡	414-220-3
FAO Specification ‡ (including year of publication)	No specification exists
Minimum purity of the active substance as manufactured ‡ (g/kg)	975 g/kg
Identity of relevant impurities (of toxicological, environmental and/or other significance) in the active substance as manufactured (g/kg)	Cyanamide 0.5 g/kg (*provisional limit*)
Molecular formula ‡	$C_{12}H_{13}N_3$
Molecular mass ‡	199.28 g/mol
Structural formula ‡	

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

Physical-chemical properties (Annex IIA, point 2)

Melting point (state purity) ‡	96.3 °C (purity: 99.4%)
Boiling point (state purity) ‡	Not measurable.
Temperature of decomposition	189.54 °C – 344.74 °C.
Appearance (state purity) ‡	Technical material: White crystalline powder (purity: 99.6% w/w)
Relative density (state purity) ‡	D^{20}_4 =1.190 [purity: 99.6% (w/w)]
Surface tension	61.51 mN m^{-1} at 20 °C (90% saturated aqueous solution)
Vapour pressure (in Pa, state temperature) ‡	1.1 x 10^{-3} Pa at 20°C (purity: 99.4%)
Henry's law constant (Pa m^3 mol^{-1}) ‡	K_H = 3.6 x 10^{-3} Pa m^3 mol^{-1}
Solubility in water ‡ (g/l or mg/l, state temperature)	pH 4.2: 0.160 g/L at 20° C (purity: 99.4%) pH 6.1: 0.121 g/L at 25° C pH 9.9: 0.099 g/L at 20° C
Solubility in organic solvents ‡ (in g/l or mg/l, state temperature)	Solvent solubility at 20 °C [g/L] n-Hexane 23.7 Toluene 412.3 CH_2Cl_2 1000.2 CH_3OH 175.9 Acetone 388.8 Ethylacetate 616.9 (purity: 99.4% w/w or 98.8%)
Partition co-efficient (log POW) ‡ (state pH and temperature)	2.84 (shaking flask method) 3.00 (HPLC method) no dependence on pH (purity: 99.4%)
Hydrolytic stability (DT_{50}) ‡ (state pH and temperature)	pH 5: no decay pH 7: DT_{50} = 2.72 year pH 9: DT_{50} = 1.86 year (22 °C)
Dissociation constant ‡	pKa = 3.52 at 20 °C

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

UV/VIS absorption (max.) ‡ (if absorption > 290 nm state ε at wavelength)	Wavelength [nm] / molar absorption coefficient [L*mol^{-1}*cm^{-1}] neutral medium: MeOH 205 *) 16280 211 sh 13450 229 sh 4870 271 27200 acid medium: 0.1 M aqueous HCl / methanol (1/9 v/v) 205 *) 16450 245 sh 12260 260 14620 317 5300 *) extinction value at 205 nm, no maximum
Photostability (DT_{50}) ‡ (aqueous, sunlight, state pH)	No significant degradation observed at pH 5, 7 and 9
Quantum yield of direct phototransformation in water at Σ > 290 nm ‡	Not calculated as no degradation was observed.
Flammability ‡	Not 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 Region (Northern or Southern Europe)	Product name	F, G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks
					Type (d–f)	Conc. of a.s. (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg a.s./hL min max	water L/ha min max	kg a.s./ha min max		
Grapes (wine)	Northern and Southern Europe	Scala	F	*Botrytis cinerea*	SC	400 g/L	Foliar spray	62 - 81	1	–	0.025 – 0.2	150 – 2000	up to 1	21	[1]
Apples	Northern and Southern Europe	Scala	F	*Venturia inaequalis resp.*	SC	400 g/L	Foliar spray	before 59 and after 71	5#)	7 – 10 d	0.03 – 0.12	500 – 2000	0.6	56	[1][2]
Protein peas	Northern Europe	Scala	F	*Botrytis spp.*	SC	400 g/L	Foliar spray	61 - 67	2	15 d	0.2 – 0.4	150 – 300	0.3 – 0.6	28	[1]

#) 3 applications at 0.6 kg a.s./ha before end of flowering and 2 applications at 0.4 kg a.s./ha after fruit formation
[1] The risk assessment has revealed a data gaps in section 5.
[2] The risk assessment has revealed a risk (exceedance of relevant threshold) in section 5.

Remarks:				
	*	Uses for which risk assessment could not been concluded due to lack of essential data 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)	(k)	The minimum and maximum number of application possible under practical conditions of use must be provided
	(e)	GCPF Codes - GIFAP Technical Monograph No 2, 1989		
	(f)	Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench	(l)	PHI - minimum pre-harvest interval
	(g)	All abbreviations used must be explained	(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)	Reversed phase HPLC with acetonitrile/water/ammonium acetate as mobile phase and UV detection at 268 nm, external standard calibration.
Impurities in technical as (principle of method)	1) Reversed phase stationary phase HPLC with acetonitrile/phosphoric acid as mobile phase and detected by UV-absorption at 210 and 236 nm 2) Reversed phase HPLC with acetonitrile/water as mobile phase and UV detection at 198 nm 3) Photometric determination at 550 nm 4) Head space GC-FID detection (solvents) 5) Determination by ion chromatography with conductivity detection
Plant protection product (principle of method)	Reversed phase HPLC with acetonitrile/water/ as mobile phase and UV detection at 230 nm, internal standard calibration.

Analytical methods for residues (Annex IIA, point 4.2)

Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	Extraction with acetone, solvent partition, silica solid phase extraction, quantification by gas chromatography with mass selective detection. LOQ = 0.05 mg/kg for potatoes, carrots, tomatoes, green beans, lettuce, sweet peppers, strawberries, raspberries, apples, grapes, bananas, grain and straw.
	Multi-residue enforcement method (DFG S19): GC-MS for determination and GC-MS/MS for confirmation LOQ = 0.01 mg/kg for cereal grain, peas, whole oranges and oilseed rape seed
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	No analytical method is required as no MRLs and no residue definition for food of animal origin is proposed
Soil (principle of method and LOQ)	LC/MS/MS LOQ = 0.01 mg/kg for pyrimethanil and LOQ = 0.01 mg/kg for AE F132593
Water (principle of method and LOQ)	LC/MS/MS LOQ = 0.05 µg/L (drinking water and surface water)
Air (principle of method and LOQ)	LC/MS/MS LOQ = 0.340 ng/L

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

Body fluids and tissues (principle of method and LOQ)	Analytical method is not required since pyrimethanil is not classified as toxic or very toxic

Classification and proposed labelling (Annex IIA, point 10)

with regard to physical/chemical data	No classification required

‡ 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 ‡	Rapid but limited to 81 and 72% (based on urinary excretion) after single and repeated oral dose (rat studies)
Distribution ‡	Widely distributed (highest levels found in adrenals, blood, liver, kidney, thyroid, ovaries and renal fat)
Potential for accumulation ‡	No potential for accumulation
Rate and extent of excretion ‡	Rapid, 95% (single low dose) and > 90% (multiple low dose) resp. within 24 hours, mainly via urine
Metabolism in animals ‡	Extensively metabolized; major metabolic pathway oxidation on both rings of the molecule to form phenols and subsequently conjugation
Toxicologically significant compounds ‡ (animals, plants and environment)	Pyrimethanil

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral ‡	4149(♂), 5971(♀) mg/kg bw
Rat LD_{50} dermal ‡	> 5000 mg/kg bw
Rat LC_{50} inhalation ‡	> 1.98 mg/L (4 hours, nose only) (max. attainable concentration)
Skin irritation ‡	Not irritating
Eye irritation ‡	Not irritating
Skin sensitization ‡ (test method used and result)	Not sensitizing (M & K test, Buehler test)

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect ‡	Liver (increased organ weight, hepatocyte hypertrophy), thyroid (follicular epithelial hypertrophy, pigment deposits), in dogs decreased water intake
Lowest relevant oral NOAEL / NOEL ‡	5.4 mg/kg bw/day, 90-day rat
Lowest relevant dermal NOAEL / NOEL ‡	No data – not required
Lowest relevant inhalation NOAEL / NOEL ‡	No data – not required

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

Genotoxicity ‡ (Annex IIA, point 5.4)

	No evidence of a genotoxic potential

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

Target/critical effect ‡	Liver (biochemistry, increased organ weight, hypertrophy), thyroid (follicular epithelial hypertrophy, pigment deposits, focal hyperplasia);
Lowest relevant NOAEL / NOEL ‡	17 mg/kg bw/day, 2 year rat
Carcinogenicity ‡	Overall no evidence of a carcinogenic potential

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction target / critical effect ‡	Reduced body weight and retarded weight gain of pups at parental toxic dose
Lowest relevant reproductive NOAEL / NOEL ‡	18.4 mg/kg bw/day for parental and reproductive toxicity
Developmental target / critical effect ‡	Fetal effects (decreased pup weight and increased incidence of 13^{th} vertebra and ribs) at maternal toxic dose no evidence of teratogenic potential
Lowest relevant developmental NOAEL / NOEL ‡	Maternal and developmental 45 mg/kg bw/day in the rabbit

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

	No data – no concern from other studies

Other toxicological studies ‡ (Annex IIA, point 5.8)

Mechanistic studies:	Induction of increased thyroid hormone clearance by enhanced hepatic metabolism resulting in chronic stimulation of thyroid gland
Metabolite AEF132593 (soil metabolite):	acute oral rat LD_{50} 735 mg/kg bw no evidence of genotoxic activity (Ames test)

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

Medical data ‡ (Annex IIA, point 5.9)

Available data indicate no detrimental effects on health of plant personnel in manufacturing of pyrimethanil; no clinical cases or poisoning incidents have been reported

Summary (Annex IIA, point 5.10)	Value	Study	Safety factor
ADI ‡	0.17 mg/kg bw/day	Overall NOAEL from 90 day and 2 year rat study, supported by multigeneration study in rats	100
AOEL ‡	0.12 mg/kg bw/day	Overall NOAEL from 90 day and 2 year rat study; (correction for 72 % enteral resorption)	100
ARfD ‡ (acute reference dose)	Not allocated – not necessary		

Dermal absorption (Annex IIIA, point 7.3)

SCALA (SC) 400 g pyrimethanil/L	1% for the concentrate 20% for the spray dilution Based on *in vitro* human skin data (24 hour exposure); supported by results of a mathematical skin permeation model considering physical/chemical parameters of the substance

Acceptable exposure scenarios (including method of calculation)

	POEM	% of AOEL
Operator	(Tractor, field peas, PPE)	75.4
	(Tractor, grapes, PPE)	121.1
	(Tractor, apples, PPE)	72.5
	(handheld, grapes, PPE)	70.0
	BBA	
	(Tractor, field peas, PPE)	58.6
	(Tractor, grapes, PPE)	47.1
	(Tractor, apples, PPE)	28.2
	(handheld, grapes, PPE)	44.0

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

Workers	Estimated exposure below the AOEL (without PPE)
Bystanders	Estimated exposure below the AOEL

Classification and proposed labelling (Annex IIA, point 10)

with regard to toxicological data	No classification proposed

‡ 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	Carrots (root vegetables), tomatoes, apples, grapes (fruits), lettuce (leafy crops) (all studies considered acceptable)
Rotational crops	Lettuce, radish, wheat (confined study with radioactive substance) lettuce, cauliflower, curly kale, wheat (field study)
Plant residue definition for monitoring	Parent compound (Pyrimethanil)
Plant residue definition for risk assessment	Parent compound (Pyrimethanil)
Conversion factor (monitoring to risk assessment)	--

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

Animals covered	Lactating cow (but identification of residues was not carried out in muscle and fat, due to low radioactivity levels in the individual extracts [<0.01 mg/kg])
Animal residue definition for monitoring	Not assessed, no residue expected at measurable level under practical conditions
Animal residue definition for risk assessment	Not assessed, no residue expected at measurable level under practical conditions
Conversion factor (monitoring to risk assessment)	--
Metabolism in rat and ruminant similar (yes/no)	--
Fat soluble residue: (yes/no)	--

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

Rotational crop study using radiolabelled material; field tests	No residues in succeeding crops to be expected above 0.05 mg/kg (based on field studies)

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

……	Stable for 9 – 12 months (carrots, lettuce, apples, tomatoes, grapes, wine, dried peas)

‡ 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)

Intakes by life stock ≥ 0.1 mg/kg diet/day:	Ruminant: yes: beef cattle: 0.23 mg/kg; dairy cattle: 0.12 mg/kg.	Poultry: yes: 0.11 mg/kg	Pig: yes: 0.14 mg/kg
Muscle	Study available. At the nominal dose rate of 1mg pyrimethanil/kg, residues of pyrimethanil, C 614276 and C 614277 are all below 0.01 mg/kg in all tissues	No data	No data
Liver		No data	No data
Kidney		No data	No data
Fat		No data	No data
Milk			
Eggs		No data	

‡ 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 Mediterranean Region	Trials results relevant to the critical GA [mg pyrimethanil/kg] (a)	Recommendation / comments	MRL[1] [mg/kg]	STMR[1] [mg/kg] (b)
Apples	Northern Region	0.12, 2 x 0.18, 0.20, 0.22, 0.30, 0.33, 0.45, 0.6		1	0.22
	Southern Region	<0.05, 0.11, 0.15, 2 x 0.16, 0.18, 0.22, 0.30, 0.37		0.5	0.16
Wine grapes	Northern Region	0.37. 0.38, 0.44, 0.59, 0.83, 0.84, 0.97, 2 x 1.1		2	0.83
	Southern Region	0.28, 0.38, 0.41, 0.42, 0.48, 0.58, 0.83, 2 x 1.0, 1.5, 2 x 1.6, 1.98		3	0.83
Peas	Northern Region	3 x <0.05, 0.061, 0.083, 0.09, 0.12, 0.3	Intended in the Northern Region only; feed item	0.3	0.072

(1) Residues expressed as mg Pyrimethanil (according to residue definition)
(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	0.17 mg/kg bw/d
TMDI (European Diet) (% ADI)	TMDI (European diet): 3.3 % ADI TMDI (German diet, girl of 13.5 kg bw): 1.8 % TMDI (UK diet, school children of 30 kg bw): 2.6 % TMDI (UK diet; infants of 7.5 kg bw): 5.9 %
NEDI (% ADI)	--
Factors included in NEDI	--
ARfD	Not regarded necessary
Acute exposure (% ARfD)	Not assessed

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

Crop/processed crop	Number of studies	Transfer factor		% Transference *
Grapes: wine	52 trials	0.08 – 0.97 one trial showing a transfer factor of 2.86 (this value seems to be rather doubtful since it is the only value above 1) Mean: 0.43 (mean of 49 plausible values		-[#]
Apples: peel pomace pomace (heat treatment) puree puree (heat treatment) juice juice (heat treatment) press cake press cake (heat treatment)	4 trials	 1.18 – 2.9 0.57 – 0.73 0.67 0.36 – 1.02 0.38 – 0.98 0.43 – 1.0 0.39 – 1.38 0.62 – 2.0 0.51 – 2.29	Mean: 1.91 0.65 0.67 0.69 0.68 0.62 0.72 1.2 1.4	-[#]

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

[#] The % of transference is not given in the corresponding studies

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

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

apples	1 mg/kg[1]
wine grapes	3 mg/kg[1]
fodder peas	0.3 mg/kg[1]

1) Pyrimethanil according to residue definition

‡ 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 ‡	After 90-105 d: Phenyl ring labelled ^{14}C-Pyrimethanil: 5.9 - 7.1 % AR Pyrimidinyl ring labelled ^{14}C-Pyrimethanil: 4.2 - 6.5 % AR
Non-extractable residues after 100 days ‡	After 90-105 days: Phenyl ring labelled ^{14}C-Pyrimethanil: 42 - 46 % AR Pyrimidinyl ring labelled ^{14}C-Pyrimethanil: 49 - 62 % AR
Relevant metabolites - name and/or code, % of applied ‡ (range and maximum)	2-amino-4,6-dimethylpyrimidine (AE F132593 = ZK 512723 = SN 512723 = NC 12723) Max. 11.5 % AR (day 105)

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

Anaerobic degradation ‡	Very low degradation of Pyrimethanil under anaerobic conditions. Major metabolite: 2-amino-4,6-dimethylpyrimidine Max. 13.6 % AR (day 30 = day 0 after water logging)
Soil photolysis ‡	Pyrimethanil was rapidly degraded by direct photolysis from soil surfaces with no single significant metabolite being formed.

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

Method of calculation	TopFit 2.0 (3-compartment model or 1-compartment model) Pyrimethanil: r^2 = 0.95 - 0.99; n = 4
Laboratory studies ‡ (range or median, with n value, with r^2 value)	DT_{50lab} (20°C, aerobic): 27.9 - 71.8 d; Mean: 52.5 d; median: 55.2d
	DT_{90lab} (20°C, aerobic): 93 – 238 d; Mean: 174.5 d; median: 183.5 d
	DT_{50lab} (10°C, aerobic): 59 – 158 d; Mean: 112 d (From 20° C lab. studies with a Q_{10} of 2.2)
	DT_{50lab} (20°C, anaerobic): >300 d

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

	Degradation in the saturated zone ‡: no data; no significant leaching of Pyrimethanil expected
Relevant metabolite	2-amino-4,6-dimethylpyrimidine (AE F132593): TopFit 2.0 (3-compartment model): r^2 = 0.95; n = 1 DT_{50lab} (20°C, aerobic): 85.5 d TopFit 2.0 (1-compartment model): 0.97-0.99; n=5 DT_{50lab} (20°C, aerobic): 15 - 100 d Overall mean: 58.3 d; median: 60.3 d
	TopFit 2.0 (3-compartment model): r^2 = 0.95; n = 1 DT_{90lab} (20°C, aerobic): 284 d TopFit 2.0 (1-compartment model): 0.97-0.99; n= 5 DT_{90lab} (20°C, aerobic): 49 - 331 d; Overall mean: 193 d; median: 200 d
Field studies (state location, range or median with n value)	4 trials in Germany single exponential 1st order kinetics DT_{50f}: 23 - 54 d; Mean: 34 d (median: 29.5) r^2: 0.71 - 0.83 (mean: 0.84)
	DT_{90f}: 82 - 180 d; Mean: 114 d (median: 97.5 d)
Soil accumulation and plateau concentration ‡	Pyrimethanil is not expected to accumulate in soil

Soil adsorption/desorption (Annex IIA, point 7.1.2)

K_f /K_{oc} ‡ K_d ‡	<u>Pyrimethanil</u> labelled at the phenyl side: 5 soils: K_{OC}: 75-500, mean: 301 K_f: 2.51-7.83 mean: 3.97 1/n: 0.85-0.90 mean: 0.868 <u>Pyrimethanil</u> labelled at the pyrimidinyl side: 4 soils: K_{OC}: 299-751, mean: 569 K_f: 3.95-23.4 mean: 13.9 1/n: 0.833-0.907 mean: 0.8595 Overall mean K_{OC}: 419 (median: 342) <u>2-amino-4,6-dimethylpyrimidine (AE F132593)</u> 6 soils: K_{OC}: 56-240, mean: 144 K_f: 1.24-5.2 mean: 2.85 1/n: 0.696-0.819 mean: 0.7787
pH dependence ‡ (yes / no) (if yes type of dependence)	Slight tendency of increasing adsorption with decreasing pH can be seen for both the active substance and metabolite AE F 132593. This dependency was not considered relevant for the assessment and was not considered in the modeling.

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

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

Column leaching ‡	Pyrimethanil (phenyl ring labelled): 4 soils Max. 1.5% AR in the leachates, identified as parent in two of the soils. No characterisation possible in the other two soils due to the low concentration of radiolabelled material. Pyrimethanil formulated as SCALA (CQ 1294): 3 soils 0.1-0.2% of the applied parent compound detected in the leachates.
Aged residues leaching ‡	Pyrimethanil (pyrimidinyl ring labelled): 1 soil (sand); ageing period 49 days Max. 3.7% AR in the leachates. Extractable radioactivity in leachates (only 0.47% AR were extractable) was identified as parent and 2-amino-4,6-dimethylpyrimidine.
Lysimeter/ field leaching studie ‡	Pyrimethanil (pyrimidinyl ring labelled) with the blank formulation CQ 1294-03 (SC-40) as carrier substance. Application rates: Two 4 years old vine plants per lysimeter (Germany) were sprayed three times between July and August in the 1st year (total amount: 1.3 - 1.7 kg a.s./ha/y), in one of the two lysimeters (lysimter 1) these applications were repeated in the 2nd year. Grape vine cultivation without further spraying of the test substance was continued in the 3rd year until end of experiment. Findings: Lys. 1: 1st y.: 0.62 µg/l ai equival. in leachate (0.12% AR) 2nd y.: 0.85 µg/l ai equival. in leachate (0.05 % AR) 3rd y.: 0.52 µg/l ai equival. in leachate (0.04 % AR) Lys. 2: 1st y.: 0.50 µg/l ai equival. in leachate (0.09% AR) 2nd y.: 0.40 µg/l ai equival. in leachate (0.05 % AR) 3rd y.: 0.26 µg/l ai equival. in leachate (0.04 % AR) Pyrimethanil (LOD 0.01 µg/l) was not detected in the leachates. Radioactivity in the leachates consisted of CO_2, non-extractables (from the water phase) and unknown polars. Radioactivity remaining on plants was in total 5.3% in the 1st year and 15.4% in the 2nd year (lysimeter 1), 13.5% in the 1st year in lysimeter 2. Radioactivity in grapes <5% AR.

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

PEC (soil) (Annex IIIA, point 9.1.3)

Parent

Method of calculation	$PEC_s(t) = \sum_{i=1}^{n} PEC_{s,\ init,\ i} \bullet e^{-k(t-t_i)}$ $TWAC_{1\ day}(T_j) = \frac{PEC(T_{j-1}) + PEC(T_j)}{2} \bullet (T_j - T_{j-1})$ $TWAC_{m\ days}(T_j) = \frac{1}{m} \bullet \sum_{k=1}^{m} TWA_{1\ day}(T_{j+1-k})$
Application rate	Pyrimethanil: 3 x 600 g/ha before flowering and 2 x 400 g/ha after first fruit formation 2-amino-4,6-dimethylpyrimidine (AE F132593): 3 x 42.8 g/ha and 2 x 28.5 g/ha → application rate adjusted for max. amount of metabolite found in laboratory soil degradation studies (11.5% AR) and for molecular weight. Plant interception: 50% in spring and 80% in summer Mixing depth: 5 cm Soil bulk densitiy: 1.5 g/cm^3 Dissipation half-life in soil: Pyrimethanil: 54 d as worst case field DT_{50} AE F132593: was not detected in the field, therefore PEC_{max} was estimated from the LOD

PEC $_{(s)}$ mg/kg	Multiple application Actual	Multiple application Time weighted average	Multiple application Actual
	Pyrimethanil		AE F132593
initial (after 1st application)	0.400	0.400	0.029
initial (after 3rd application) = peak concentration	1.100	1.100	<0.10
short term 24 h	1.086	1.093	
2 d	1.072	1.086	
4 d	1.045	1.072	

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

PEC $_{(s)}$ mg/kg		Multiple application Actual	Multiple application Time weighted average	Multiple application Actual
		Pyrimethanil		AE F132593
long term	7 d	1.006	1.052	
	28 d	0.769	0.925	
	50 d	0.580	0.813	
	100 d	0.410	0.632	

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

Hydrolysis of active substance (DT_{50}) (state pH and temperature)		pH 5 (22°): > 1 y pH 7 (22°): 2.74 y pH 9 (22°): 1.86 y
Hydrolysis of relevant metabolites (DT_{50}) (state pH and temperature)		Not relevant
Photolytic degradation of active substance (DT_{50})		pH 5, 7 and 9: stable pH 4: 29 h (indirect photolysis due to photosensitiser)
Photolytic degradation of relevant metabolites		Not relevant
Readily biodegradable (yes/no)		No
Degradation in water/sediment	-DT_{50} water -DT_{90} water	8.9 d and 24 d 99 d and 79 d
	-DT_{50} whole system -DT_{90} whole system	121 d and 40 d not stated and 134 d
Mineralization		Max. 2.4 % and 9.1 % CO_2 production after 100 d
Non-extractable residues		Max. 27.3 % and 47.7% after 100 d
Distribution in water/sediment systems (active substance)		Pyrimethanil declined in waterphase (min. 8.6 and 3.4 % after 100 d) and increased in sediment (system 1: max. 68 % after 30 d; system 2: max. 46.7 % after 14 d) and decreased in sediment by the end of the test (system 1: 42.8 %; system 2: 12.5 % after 100 d)
Distribution in water/sediment systems (metabolites)		2-amino-4,6-dimethylpyrimidine (AE F132593) in water: system 1: max. 2.4 %, system 2: max 6 % after 100 d 2-amino-4,6-dimethylpyrimidine (AE F132593) in sediment: system 1: max. 3.7 %, system 2: max 4.4 % after 100d

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

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

Parent

Method of calculation	TopFit 2.0 computer program
Main routes of entry	spray drift, German Spray Drift Tables, with overall 90th percentile worst case for total application sequence
depth of water body / of sediment	0.3 m / 0.05 m (bulk density of sediment: 0.8 g/cm³)
behaviour in surface water systems	described by set of reaction rate constants that were derived by a kinetic evaluation of the worst-case water/sediment study (i.e. with the highest concentrations in the water or in the sediment): PECsw: calculated with rate constants from system 2 PECsed: calculated with rate constants from system 1
Application rate (worst case-application schemes according to GAP)	vine: 1000 g/ha apples: 3 x 600 g/ha before flowering (interval 7 d) 2 x 400 g/ha after first fruit formation (interval 7 d) peas: 2 x 600 g /ha (interval 15 d)

PEC $_{(sw)}$ Vine µg/L		Single application Actual	Single application TWA	Single application Actual	Single application TWA	Single application Actual	Single application TWA
		Distance: 3 m Drift rate: 8.02 %		Distance: 5 m Drift rate: 3.62 %		Distance: 10 m Drift rate: 1.23 %	
initial		26.733	26.733	12.067	12.067	4.100	4.100
short term	24 h	21.909	24.321	9.889	10.978	3.360	3.730
	2d	18.765	22.329	8.470	10.079	2.878	3.425
	4d	15.317	19.599	6.914	8.847	2.349	3.006
long term	7 d	13.247	17.254	5.979	7.788	2.032	2.646
	14 d	11.662	14.791	5.264	6.676	1.789	2.268
	28 d	9.799	12.744	4.423	5.752	1.503	1.954
	42 d	8.251	11.497	3.724	5.189	1.265	1.763
Plateau concentrations		-	-	-	-	-	-

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

PEC $_{(sw)}$ Apples µg/L		Multiple application Actual	Multiple application TWA	Multiple application Actual	Multiple application TWA	Multiple application Actual	Multiple application TWA
		Distance: 3 m Drift rate: 23.12 %		Distance: 10 m Drift rate: 8.42 %		Distance: 20 m Drift rate: 2.09 %	
initial		89.31	89.31	32.53	32.53	8.074	8.074
short term	24 h	80.10	84.71	29.17	30.85	7.241	7.657
	2d	73.92	80.86	26.92	29.45	6.683	7.309
	4d	66,71	75.43	24.30	27.47	6.031	6.819
long term	7 d	61.56	70.47	22.42	25.66	5.565	6.370
	14 d	55.59	64.40	20.25	23.45	5.026	5.821
	28 d	46.77	57.72	17.03	21.02	4.228	5.218
	42 d	39.38	52.81	14.34	19.23	3.560	4.773
Plateau concentrations		-	-	-	-	-	-

PEC $_{(sw)}$ Peas µg/L		Multiple application Actual	Multiple application TWA	Multiple application Actual	Multiple application TWA	Multiple application Actual	Multiple application TWA
		Distance: 1 m Drift rate: 2.38 %		Distance: 5 m Drift rate: 0.47 %		Distance: 10 m Drift rate: 0.24 %	
initial		6.809	6.809	1.345	1.345	0.687	0.687
short term	24 h	5.925	6.367	1.170	1.257	0.597	0.642
	2d	5.340	5.999	1.054	1.185	0.538	0.605
	4d	4.677	5.488	0.924	1.084	0.472	0.553
long term	7 d	4.237	5.034	0.837	0.994	0.427	0.508
	14 d	3.800	4.515	0.750	0.892	0.383	0.455
	28 d	3.169	4.001	0.631	0.790	0.322	0.403
	42 d	2.691	3.646	0.531	0.720	0.271	0.368
Plateau concentrations		-	-	-	-	-	-

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

Metabolite

Method of calculation	The PEC_{sw} of the main metabolite 2-amino-4,6-dimethylpyrimidine (AE F132593) was not calculated separately because of its very low toxicity and its low concentration in the water and sediment phase of the water/sediment study. The PEC value for TER calculation was based on the worst case assumption that the parent was immediately and completely transformed to AE F132593 and therefore is equal to the concentration of the parent compound at every time point.

PEC (sediment)

Parent

Method of calculation	See above
Application rate	See above

$PEC_{(sed)}$	max. PEC_{sed} [µg/kg])					
	1 m	3 m	5 m	10 m	15 m	20 m
apples at day 130 after 1st application	-	770.5	501.5	280.6	153.6	69.7

Metabolite

Method of calculation	The PEC_{sed} of the main metabolite 2-amino-4,6-dimethylpyrimidine (AE F132593) was not calculated separately because of its very low toxicity and its low concentration in the water and sediment phase of the water/sediment study. The PEC value for TER calculation was based on the worst case assumption that the parent was immediately and completely transformed to AE F132593 and therefore is equal to the concentration of the parent compound at every time point.

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

Method of calculation and type of study (*e.g.* modelling, monitoring, lysimeter)	FOCUS PELMO 1.1.1
Application rate	3 x 300 g a.s./ha (= 50% interception) on apples with the 1st application at plant stage BBCH 10 and 7 d interval between the applications plus 2 x 80 g a.s./ha (= 80% interception) at the date of

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

	harvest, with 7 d interval between the applications. Input parameters: Pyrimethanil: K_{OC}: 419; 1/n: 0.86; Formation metabolites:k_{12} (AE F132593): 0.00235; k_{13} (NER, CO_2, minor m.): 0.01643, which gives an DT_{50} of 37 days. AE F132593: K_{OC}: 143; 1/n: 0.78; k: 0.00962 (corresponds to a DT_{50} of 72 days).

$PEC_{(gw)}$

Maximum concentration	Not reported.
Average annual concentration (Results quoted for modelling with FOCUS gw scenarios, according to FOCUS guidance)	Annual 80th percentile worst case concentrations at 1 m depth Pyrimethanil: <0.001 µg/l in all FOCUS scenarios AE F132593: <0.001 µg/l in all FOCUS scenarios except "Piacenza" (0.004 µg/l predicted)

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

Direct photolysis in air ‡	Not available
Quantum yield of direct phototransformation	Not available for air. Zero for aqueous photolysis
Photochemical oxidative degradation in air ‡	According to the method of Atkinson: DT_{50} = 1.8 hours
Volatilization ‡	From plant surfaces: 27% within 24 hours from soil: ca. 10% within 24 hours

PEC (air)

Method of calculation	Not applicable

$PEC_{(a)}$

Maximum concentration	With a vapour pressure of 2.2 x 10-3 Pa (25°C) and a Henry constant of 3.6 x 10-3 Pa x m3/mol Pyrimethanil shows some tendency for volatilisation. This was confirmed by volatilisation experiments. Due to its fast degradation in air no significant concentrations are expected in the atmosphere.

‡ 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	Soil Definitions for risk assessment: pyrimethanil, 2-amino-4,6-dimethyl-pyrimidine- Definitions for monitoring: pyrimethanil, 2-amino-4,6-dimethyl-pyrimidine (pending assessment of effects on micro-organisms and long term toxicity to earthworms) Water Ground water Definitions for exposure assessment: pyrimethanil, 2-amino-4,6-dimethyl-pyrimidine- Definitions for monitoring: pyrimethanil Surface water Definitions for risk assessment: pyrimethanil Definitions for monitoring: pyrimethanil Air Definitions for risk assessment: pyrimethanil Definitions for monitoring: pyrimethanil

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

Soil (indicate location and type of study)	--
Surface water (indicate location and type of study)	--
Ground water (indicate location and type of study)	--
Air (indicate location and type of study)	--

Classification and proposed labelling (Annex IIA, point 10)

with regard to fate and behaviour data	R 53 (proposed) 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} 4149 (♂) / 5971 (♀)mg a.s./kg bw (rat)
Acute toxicity to birds ‡	LD_{50} > 2000 mg a.s./kg bw (bobwhite quail and mallard)
Dietary toxicity to birds ‡	LC_{50} > 5200 ppm ≅ LD_{50} > 873.6 mg a.s./kg bw (bobwhite quail)
Reproductive toxicity to birds ‡	NOAEC 1000 ppm ≅ NOAEL 95.96 mg a.s./kg bw (bobwhite quail)
Reproductive toxicity to mammals	NOAEC 400 ppm ≅ NOAEL 18.4 (♂) / 23.4 (♀) mg a.s./kg bw (2-gen. rat)

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

Application rate (kg a.s./ha)	Crop	Category (e.g. insectivorous bird)	Time-scale	TER	Annex VI Trigger
birds, tier 1					
1	grapes	herbivorous bird	acute	> 106	10
		insectivorous bird		> 37	10
5 x 0.6	apples	insectivorous bird		> 62	10
2 x 0.6	peas	herbivorous bird		> 43	10
		insectivorous bird		> 62	10
1	grapes	herbivorous bird	short-term	> 87	10
		insectivorous bird		> 29	10
5 x 0.6	apples	insectivorous bird		> 48	10
2 x 0.6	peas	herbivorous bird		> 35	10
		insectivorous bird		> 48	10
1	grapes	herbivorous bird	long-term	18	5
		insectivorous bird		3.2*	5
5 x 0.6	apples	insectivorous bird		5.3	5
2 x 0.6	peas	herbivorous bird		7.3	5
		insectivorous bird		5.3	5
*considered addressed based on a weight of evidence approach					

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

Application rate (kg a.s./ha)	Crop	Category (e.g. insectivorous bird)	Time-scale	TER	Annex VI Trigger
mammals, tier 1					
1	grapes	small herbivorous mammal	acute	69	10
5 x 0.6	apples	small herbivorous mammal		37	10
2 x 0.6	peas	medium herbivorous mammal		237	10
1	grapes	small herbivorous mammal	long-term	1.1	5
		medium herbivorous mammal		5.4	5
5 x 0.6	apples	small herbivorous mammal		0.5	5
		medium herbivorous mammal		2.3	5
2 x 0.6	peas	medium herbivorous mammal		3.8	5
mammals, refinement 1 (measured residue decline on plants considered)					
1	grapes	small herbivorous mammal	long-term	3.4	5
5 x 0.6	apples	small herbivorous mammal		1.3	5
		medium herbivorous mammal		6.5	5
2 x 0.6	peas	medium herbivorous mammal		11.6	5
mammals, refinement 2 (refinement of relevant toxicity endpoint)					
1	grapes	small herbivorous mammal	long-term	8.2	5
5 x 0.6	apples	small herbivorous mammal		3.2	5
mammals, refinement 3 (refinement of PD of crop-relevant small rodent)					
5 x 0.6	apples	small rodent, mixed diet	long-term	12	5

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/l)
Laboratory tests ‡				
Rainbow trout	pyrimethanil	96 h	LC_{50}	10.56
Daphnia	pyrimethanil	48 h	EC_{50}	2.9
Green alga	pyrimethanil	96 h	E_bC_{50}/E_rC_{50}	1.2/5.84
Rainbow trout	AE F132593	96 h	LC_{50}	> 100
Daphnia	AE F132593	48 h	EC_{50}	> 100
Greenalgae	AE F132593	96 h	E_bC_{50} and E_rC_{50}	> 100

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

Group	Test substance	Time-scale	Endpoint	Toxicity (mg/l)
Rainbow trout	Scala	96 h	LC_{50}	19.0
Daphnia	Scala	48 h	EC50	3.8
Green alga	Scala	96 h	EbC50/ErC50	7.1/13.1
Rainbow trout	pyrimethanil	91 d	NOEC (growth)	Study requested
Daphnia	pyrimethanil	21 d	NOEC (reproduction)	0.94
Chironomus	pyrimethanil	28 d	NOEC (emergence)	4.0
Daphnia	Scala	21 d	NOEC (reproduction)	0.3
Microcosm or mesocosm tests: not required				

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

Application rate (g as/ha)	Crop	Organism	Time-scale	Distance (m)	TER	Annex VI Trigger
pyrimethanil						
1 x 1000	vine	Rainbow trout	acute	3	395	100
3 x 600 2 x 400	apples	Rainbow trout	acute	3	118	100
2 x 600	peas	Rainbow trout	acute	1	1551	100
1 x 1000	vine	Daphnia	acute	3	109	100
3 x 600 2 x 400	apples	Daphnia	acute	10	117	100
2 x 600	peas	Daphnia	acute	1	426	100
1 x 1000	vine	Green algae	acute	3	45	10
3 x 600 2 x 400	apples	Green algae	acute	3	13	10
2 x 600	peas	Green algae	acute	1	176	10
1 x 1000	vine	Rainbow trout	chronic	-	-*	10
3 x 600 2 x 400	apples	Rainbow trout	chronic	-	-*	10
2 x 600	peas	Rainbow trout	chronic	-	-*	10
1 x 1000	vine	Daphnia	chronic	3	69	10
3 x 600 2 x 400	apples	Daphnia	chronic	3	15	10

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

Application rate (g as/ha)	Crop	Organism	Time-scale	Distance (m)	TER	Annex VI Trigger
3 x 600 2 x 400	peas	Daphnia	chronic	1	223	10
1 x 1000	vine	Chironomus	chronic	3	314	10
3 x 600 2 x 400	apples	Chironomus	chronic	3	69	10
2 x 600	peas	Chironomus	chronic	1	1000	10
* Study requested. Risk assessment can only be concluded once the new fish ELS study becomes available.						

Application rate (g as/ha)	Crop	Organism	Time-scale	Distance (m)	TER	Annex VI Trigger
Metabolite AE F132593						
1 x 1000	vine	Rainbow trout	acute	3	>3741	100
3 x 600 2 x 400	apples	Rainbow trout	acute	3	>1120	100
2 x 600	peas	Rainbow trout	acute	1	>14686	100
1 x 1000	vine	Daphnia	acute	3	>3741	100
3 x 600 2 x 400	apples	Daphnia	acute	3	>1120	100
2 x 600	peas	Daphnia	acute	1	>14686	100
1 x 1000	vine	Green algae	acute	3	>3741	100
3 x 600 2 x 400	apples	Green algae	acute	3	>1120	100
2 x 600	peas	Green algae	acute	1	>14686	100

Application rate (g as/ha)	Crop	Organism	Time-scale	Distance (m)	TER	Annex VI Trigger
SC-formulation (Scala)						
1 x 1000	vine	Rainbow trout	acute	3	711	100
3 x 600 2 x 400	apples	Rainbow trout	acute	3	213	100
2 x 600	peas	Rainbow trout	acute	1	2790	100
1 x 1000	vine	Daphnia	acute	3	142	100
3 x 600 2 x 400	apples	Daphnia	acute	10	117	100
2 x 600	peas	Daphnia	acute	1	558	100

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

Application rate (g as/ha)	Crop	Organism	Time-scale	Distance (m)	TER	Annex VI Trigger
1 x 1000	vine	Green algae	acute	3	266	10
3 x 600 2 x 400	apples	Green algae	acute	3	80	10
2 x 600	peas	Green algae	acute	1	1043	10
1 x 1000	vine	Daphnia	chronic	3	22	10
3 x 600 2 x 400	apples	Daphnia	chronic	10	14	10
2 x 600	peas	Daphnia	chronic	1	71	10

Bioconcentration

Bioconcentration factor (BCF) ‡	Study not required, log P_{ow} < 3
Annex VI Trigger:for the bioconcentration factor	--
Clearance time (CT_{50}) (CT_{90})	--
Level of residues (%) in organisms after the 14 day depuration phase	--

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

Acute oral toxicity ‡	Pyrimethanil: LD_{50} > 100 µg a.s./bee Scala: LD_{50} > 200 µg product/bee
Acute contact toxicity ‡	Pyrimethanil: LD_{50} > 100 µg a.s./bee Scala: LD_{50} > 200 µg product/bee

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

Application rate	Crop	Route	Hazard quotient	Annex VI Trigger
Laboratory tests				
1 kg a.s. / ha	grapes	oral	< 10	50
		contact	< 10	50
2.5 kg Scala / ha	grapes	oral	< 12.5	50
		contact	< 12.5	50

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

Field or semi-field tests Semi-field study on flowering *Phacelia* showed no effects at 5 L Scala/ha

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

Species	Stage	Test Substance	Dose (kg a.s./ha)	Endpoint	Effect	Annex VI Trigger
Laboratory tests						
Aphidius rhopalosiphi	adults	Scala	1	mortality fecundity	63 % 18 %	30 %
Aphidius rhopalosiphi	adults	Scala	0.04 0.111 0.333 1 3	mortality / fecundity	0 % / 59 % 23 % / 84 % 80 % / - 70 % / - 75 % / -	30 %
Encarsia formosa	adults	Scala	1	mortality fecundity	100 % (6 d) 69 %	30 %
Coccygomimus turionellae	adults	Scala	0.988	mortality fecundity	0 -8.6 %	30 %
Trichogramma cacoeciae	adults	Scala	1	mortality fecundity	99 % 100 %	30 %
Typhlodromus pyri	larvae and proto-nymphs	Scala	1.04	mortality fecundity comb.effect	38 % 52 % 68 %	30 %
Orius laevigatus	nymphs	Scala	1	mortality fecundity	4.3 % 24 %	30 %
Coccinella septempunctata	larvae until adult	Scala	1	mortality fecundity	85 % no conclusion possible	30 %
Chrysoperla carnea	larvae until adult	Scala	1	mortality	8 %	30 %
Episyrphus balteatus	larvae	Scala	1	mortality fecundity	- 7 % 4 %	30 %
Poecilus cupreus	adults	Scala	1.2	mortality feeding act.	0 2.4 %	30 %
Extended laboratory test						
Aphidius rhopalosiphi	adults	Scala	1	mortality fecundity	0 9 %	30 %

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

Species	Stage	Test Substance	Dose (kg a.s./ha)	Endpoint	Effect	Annex VI Trigger
Semi-field tests						
Trichogramma cacoeciae	adults	Scala	0.6	mortality fecundity	- 2 % - 5.7 %	-
	adults	Scala	1	mortality fecundity	3.5 % 42 %	-
Encarsia formosa	adults	Scala	2 x 1 (7d)	parasitic potential	62-70 % up to 3 d	-
	pupae	Scala	2 x 1 (7d)	mortality	0	-

Field tests

predatory mites / apple orchard, application of Scala at 5 x ca. 450 g a.s./ha: no statistically significant differences in mite densities up to 5 weeks after application

Coccinella septempunctata and other beneficial insects / apple orchard, application of Scala at 600 and 1000 g a.s./ha: no significant differences in no.s of arthropods

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

Acute toxicity ‡ Active substance	Study with parent: 14 day $LC_{50\ corr.}$: 313 mg a.s./kg soil Study with Pyrimethanil 40 SC (CQ1294/03): 14 day $LC_{50\ corr.}$: >500 mg product/kg soil (i.e. >187 mg a.s./kg)
Metabolite AE F132593	14 day LC_{50}: >1000 mg/kg soil
Reproductive toxicity ‡	Study with Pyrimethanil 40 SC (AE B100309 00 SC37 A404): $NOEC_{corr.}$: 4.12 mg/kg soil

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

Application rate (kg as/ha) *	Crop	Toxicity endpoint	Time-scale	TER	Annex VI Trigger
Active substance					
3 x 0.3	apples	$LC_{50\ corr.}$	acute	284	10
3 x 0.3	apples	$NOEC_{corr.}$	long term	3.75	5
Metabolite AE F132593					
3 x 0.3 (peak level <0.1 mg/kg for met.)	Apples	LC_{50}	acute	>10 000	10

* assuming 50% interception

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

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

Nitrogen mineralization ‡	No unacceptable effects at concentrations up to 1.08 mg a.s./kg soil
Carbon mineralization ‡	No unacceptable effects at concentrations up to 10.8 mg a.s./kg soil

Classification and proposed labelling (Annex IIA, point 10)

with regard to ecotoxicological data	N Harmful R 51 Toxic to aquatic organisms

‡ 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
CA	Chemical Abstract
CAS	Chemical Abstract Service
CIPAC	Collaborative International Pesticide Analytical Council Limited
d	day
DAR	draft assessment report
DM	dry matter
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
ε	decadic molar extinction coefficient
EC_{50}	effective concentration
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINKS	European List of New Chemical Substances
EMDI	estimated maximum daily intake
ER50	emergence rate, median
EU	European Union
FAO	Food and Agriculture Organisation of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	good agricultural practice
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GS	growth stage
ha	hectare
hL	hectolitre
HPLC	high pressure liquid chromatography or high performance liquid chromatography
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
K_{oc}	organic carbon adsorption coefficient
L	litre
LC	liquid chromatography
LC-MS	liquid chromatography-mass spectrometry
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LC_{50}	lethal concentration, median

LD_{50}	lethal dose, median; dosis letalis media
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification (determination)
µg	microgram
mN	milli-Newton
MRL	maximum residue limit or level
MS	mass spectrometry
NESTI	national estimated short term intake
NIR	near-infrared-(spectroscopy)
nm	nanometer
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
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
TMDI	theoretical maximum daily intake
UV	ultraviolet
WHO	World Health Organisation
WG	water dispersible granule
yr	year