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

prothioconazole

finalised: 12 July 2007

SUMMARY

Prothioconazole is a new active substance for which in accordance with Article 6 (2) of Council Directive 91/414/EEC[1] United Kingdom received an application from Bayer CropScience for inclusion in Annex I to Directive 91/414/EEC. Complying with Article 6 of Directive 91/414/EEC, the completeness of the dossier was evaluated and confirmed by Commission Decision 2003/35/EC[2].

Following the agreement between the EU-Commission and the EFSA for the EFSA to organise a peer review of those new active substances for which the decision on the completeness of the dossier had been published after June 2002, the designated rapporteur Member State United Kingdom made the report of its initial evaluation of the dossier on prothioconazole, hereafter referred to as the draft assessment report (DAR), available on 18 October 2004. This draft assessment report was distributed for consultation to the Member States and the notifier on 21 October 2004.

The peer review was initiated on 21 October 2004 by dispatching the draft assessment report for consultation of the Member States and the notifier. Subsequently, the comments received on the DAR were examined by the rapporteur Member State and the need for additional data was agreed during a written procedure in January 2006. Remaining issues as well as further data made available by the notifier upon request were evaluated in a series of scientific meetings with Member State experts in September 2006.

A final discussion of the outcome of the consultation of experts took place with representatives from the Member States on 25 April 2007 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 a fungicide as proposed by the applicant which comprises foliar application to wheat, rye, triticale, barley, oats and oilseed rape and as a seed treatment to the same crops excluding oilseed rape. Full details of the application rates and timings can be found in the attached end points.
There are two representative formulated products evaluated Proline an emulsifiable concentrate (EC) formulation and Redigo a flowable concentrate for seed treatment (FS) formulation.

[1] OJ No L 230, 19.8.1991, p. 1. Directive as last amended by OJ L 106, 24.4.2007, p.14
[2] OJ No L 11, 16.1.2003, p.52

Methods are available to monitor all compounds given in the respective residue definition for food of plant origin, water, soil and air. Residues in food of plant origin can be determined with a multi-method (The German S19 method has been validated for prothioconazole-desthio). Only single methods are available to determine residues of prothioconazole-desthio, in products of animal origin and prothioconazole, prothioconazole-desthio in soil water and air. A method is not available to monitor the glucuronide conjugate in products of animal origin. Also if the active is classified as toxic then methods for body fluids and tissues would need to be considered.
Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that at least some quality control measurements of the plant protection product are possible. Methods for the relevant impurities in the formulation are not available.

Prothioconazole is of low acute oral, dermal and inhalation toxicity; it does not show any eye and skin irritation or sensitising potential. The relevant short term oral NOAEL is 25 mg/kg bw/day and the chronic NOAEL is 5 mg/kg bw/day (the liver being the main target organ with increases in hepatic enzyme activity, increased liver weights and hepatocellular hypertrophy were consistent with hepatic enzyme induction). Prothioconazole does not show *in vivo* genotoxic and carcinogenic potential. The relevant reproductive NOAEL is 95.6 mg/kg bw/day, while the developmental NOAEL is 20 mg/kg bw/day. In rats, an increased incidence of microphthalmia was observed at the high dose level. The increased incidence of rudimentary supernumerary ribs at the high dose level was also considered to be treatment related. Hence, prothioconazole was proposed to be classified as Repro cat 3, R 63 (Repro cat 2?), based on the increased incidences of microphthalmia (at 1000 mg/kg, maternal toxic dose) in one out of two rat strains tested. Prothioconazole did not show toxicity to the nervous system. The proposed ADI for prothioconazole is 0.05 mg/kg bw/day, and the ARfD and AOEL are 0.2 mg/kg bw. The estimated operator exposure to the 250 EC formulation is below the AOEL when PPE is worn for mechanical spraying in cereals, using the UK-POEM and the German model. The exposure of operators working at the treatment of seeds with the prothioconazole FS formulation accounts for about 45% of the AOEL for operators performing mixing/loading/calibration/cleaning and bagging. For sowing, the estimated exposure is about 2% of the AOEL. The exposure of workers after spraying in cereals is about 45% of the AOEL. Estimated exposure of bystanders is negligible
The main metabolite prothioconazole-desthio, M04, is considered relevant. An ADI of 0.01 mg/kg bw/day was set based on the NOAEL of 1.1 mg/kg bw/day (liver histopathology and reduced weight gain in the rat carcinogenicity study), applying a 100 fold assessment factor. The ARfD was discussed in the experts' meeting: the experts agreed on the NOAEL from the rat developmental study (1 mg/kg bw/day), based on an increase in supernumerary ribs at 3 mg/kg bw/day, with a SF 100. The same value of 0.01 mg/kg bw was considered as an AOEL. M04 was toxic for the development in rats and rabbits and the classification Repro.cat.2, R61 was proposed by the experts.

The metabolism of prothioconazole has been fully investigated in cereals, oilseeds, rotational crops as well as in livestock and mainly proceeds through oxidative reactions. In most plant parts and animal

tissues, the major compound of the metabolic pattern is prothioconazole-desthio, which is more toxic than the parent compound. Given the complex plant and animal metabolic pattern and to reflect adequately the toxicological burden the consumer is exposed to, the residue definition for risk assessment in all commodities is the sum of prothioconazole-desthio and all metabolites containing the 2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl-2H-1,2,4-triazole moiety, expressed as prothioconazole-desthio.

This residue definition for risk assessment is however provisional as beside the metabolites which are structurally related to the parent compound, cereal grains, oilseeds, rotational crops and animal products are expected to contain significant amounts of non specific triazole derivative metabolites. These compounds (mainly triazole, triazole alanine and triazole acetic acid) which are common metabolites of all triazole fungicides have been recognized as hazards given their impact on reproduction. Toxicological reference values have been agreed by the PRAPeR expert meeting 14 on toxicology in January 2007.

The monitoring of plant and animal commodities can be targeted on prothioconazole-desthio, but in animal tissue, its glucuronide conjugate needs to be included in the analysis. A sufficient amount of data has been submitted in order to set MRLs.

Chronic and acute consumer exposures are well below the respective toxicological trigger values allocated to prothioconazole-desthio.

This assessment was conducted on the basis of the provisional residue definition for risk assessment and does not cover the triazole derivative metabolites. A robust conclusion on the risk for the consumer cannot be finalised at this stage. Information on the actual level of those derivatives in primary crops, rotational crops, and products of animal origin is lacking. It must be noted that this lack of data is a generic issue and concerns all active substances of the triazole chemical class whose degradation pathway in primary crops, soil and livestock involves a cleavage of the triazole ring.

The available studies on the environmental fate and behaviour of prothioconazole indicated that there is no potential for persistence or accumulation of prothioconazole and its degradation products in the environmental compartments. Prothioconazole is of low persistence in soil in both laboratory and field studies (lab DT_{50} = 0.07-1.27 days; field DT_{50} = 1.3-2.8 days, median = 1.6 day). The major metabolites formed in soil, i.e. prothioconazole-desthio (M04, max. 49.4% AR) and prothioconazole-S-methyl (M01, max. 14.6% AR), are more persistent (in laboratory studies DT_{50} for M01 = 5.9-46.0 days, and DT_{50} for M04 = 7.0-34.0 days). Under field conditions, the dissipation time for prothioconazole-desthio was estimated to be in the range of 16.3-72.3 days. In all field trials no residues of prothioconazole or of its metabolites were detected below 20 cm depth of soils. These findings confirmed the results obtained from different laboratory mobility studies, which showed that prothioconazole is of low mobility (K_{oc} = 1765 mL/g, determined in aged column leaching study), as well as prothioconazole-S-methyl and prothioconazole-desthio (K_{foc} = 1974 - 2995 mL/g and 523 - 625 mL/g, respectively). Exposure assessment with FOCUS-PELMO model indicated that no concerns related to groundwater contamination by prothioconazole or its metabolite prothioconazole-desthio (M04) and prothioconazole-S-methyl (M01) are to be expected. From soil photolysis studies, there appeared to be no significant influence of light on the rate of degradation of prothioconazole.

Prothioconazole is considered stable to hydrolysis and hydrolytic breakdown will not contribute to the degradation of prothioconazole in the aquatic environment. Whenever surface water will be contaminated by the parent compound, solar radiation may contribute to the degradation of prothioconazole via phototransformation reactions (predicted environmental half-life under June solar summer conditions of 11 days in Athens, Greece). Prothioconazole-desthio (M04) was identified as the main photolytic degradation product (max. 56% AR). Other two major degradation products were identified as prothioconazole-thiazocine (M12) at 14% AR and 1,2,4-triazole (M13) at 12% AR. Taking into account the fast dissipation of prothioconazole from the water phase (DT_{50}water = 0.8-1.0 days at 20ºC in the dark) observed in a water/sediment study, it is unlikely that prothioconazole-thiazocine (M12) will be formed at > 10% in natural surface water systems under realistic environmental conditions. 1,2,4-triazole (M13) shows no light adsorption above 290 nm and is regarded as stable to photolytic degradation in water. Prothioconazole rapidly disappeared from two aerobic natural water/sediment systems, with a calculated half-life of 1.6-2.8 days referring to the whole system. A proportion of prothioconazole partitioned quite rapidly into the sediment (max 22.6-23.4% AR in the sediment on day 1), but there is also rapid degradation to prothioconazole-desthio (M04), which can also partition into sediment (max 26.9% AR). Another metabolite exceeding 10% of the applied radioactivity in the water layer was identified as 1,2,4-triazole (M13, max. 37.2% AR). No DT_{50} values for metabolites were available. Predicted Environmental Concentration in surface water (PECsw) and sediment (PECsed) were estimated for prothioconazole, prothioconazole-desthio (M04) and 1,2,4-triazole (no PECsed calculations provided as not being a major metabolite in sediment) assuming spray drift from the maximum three recommended foliar applications.
Based on the results concerning vapour pressure, Henry Law constant and photo oxidative stability in ambient air, it can be concluded that neither emission of prothioconazole into the air, nor accumulation and contamination by wet or dry deposition are to be expected for the parent compound and its metabolite prothioconazole-desthio (M04).

The risk to birds and mammals from the use of prothioconazole as a foliar application in cereals and oilseed rape is considered to be low. The assessment of long-term risk for birds and mammals from the use as cereal seed treatment indicates a high risk based on the available and peer reviewed data and information. Risk mitigation measures to reduce spray drift input comparable to 5 m spray free buffer zones are required to protect the aquatic environment based on the currently evaluated data and information. EFSA recommends that the available full life cycle study with the metabolite prothioconazole-desthio is evaluated before a final conclusion on the risk to fish is drawn. Furthermore, bioconcentration of prothioconazole-S-methyl should be considered at Member State level should MS surface water exposure assessment show that this metabolite may contaminate surface water from drainage and/or run-off. The risk to bees, other non-target arthropods, earthworms, other non-target soil macro-organisms, soil micro-organisms, non-target plants and biological methods of sewage treatment is considered to be low.

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

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BACKGROUND

In accordance with Article 6 (2) of Council Directive 91/414/EEC United Kingdom received an application from Bayer CropScience for inclusion of the active substance prothioconazole in Annex I to Directive 91/414/EEC. Complying with Article 6 of Directive 91/414/EEC, the completeness of the dossier was evaluated and confirmed by Commission Decision 2003/35/EC.

Following the agreement between the EU-Commission and EFSA for EFSA to organise a peer review of those new active substances for which the completeness of the dossier had been officially confirmed after June 2002, the designated rapporteur Member State United Kingdom submitted the report of its initial evaluation of the dossier on prothioconazole, hereafter referred to as the draft assessment report (DAR), to EFSA on 18 October 2004. This draft assessment report was distributed for consultation to the Member States and the notifier on 21 October 2004.

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

Taking into account the information received from the notifier addressing the request for further data, a scientific discussion of the identified data requirements and/or issues took place in expert meetings organised by EFSA in September 2006. 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 25 April 2007 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).

Following the agreement between the EU Commission and EFSA regarding the peer review of new active substances, 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. 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 1 March 2006),

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. 2-1 of 27 April 2007)

Given the importance of the draft assessment report including its addendum (compiled version of March 2007 containing all individually submitted addenda) and the peer review report with respect to the examination of the active substance, both documents are considered respectively as background documents A and B to this conclusion.

THE ACTIVE SUBSTANCE AND THE FORMULATED PRODUCT

Prothioconazole is the ISO common name for (*RS*)-2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-2,4-dihydro-1,2,4-triazole-3-thione (IUPAC).

Prothioconazole belongs to the class of fungicides which are commonly referred to as the triazoles. This class of fungicides includes compounds such as epoxiconazole and flusilazole. It is a systemic fungicide with protective curative and eradicative activity. Its mode of action is steroid demethylation (ergosterol biosynthesis).

There are two representative formulated products evaluated Proline an emulsifiable concentrate (EC) formulation and Redigo a flowable concentrate for seed treatment (FS) formulation.

The evaluated representative uses were as a fungicide which comprises foliar application to wheat, rye, triticale, barley, oats and oilseed rape and as a seed treatment to the same crops excluding oilseed rape. Full details of the application rates and timings can be found in the attached end points.

SPECIFIC CONCLUSIONS OF THE EVALUATION

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

The minimum purity of prothioconazole as manufactured should not be less than 970 g/kg.
At the moment no FAO specification exists.

In the DAR the pilot plant production was evaluated subsequent to this full scale production has stabilized and new batch data and technical specification were presented in addendum 3 of Volume 4. On an analytical basis the new specifications were not considered equivalent to the pilot plant one

however, after consideration by the mammalian and ecotoxicology meetings of experts it was concluded that they are equivalent.
However, since the current specification does not include the relevant impurity prothioconazole-desthio and the level for prothioconazole–deschloro level not yet accepted by toxicology the specification for the technical material as a whole should be regarded as provisional for the moment.

The technical material contains toluene, which has to be regarded as a relevant impurity. The maximum content in the technical specification is set at 5 g/kg. In addition to this the impurity prothioconazole-desthio seen in the pilot plant batches and prothioconazole–deschloro are also considered relevant. In addendum 3 of Volume 4 it appeared that the relevant impurity prothioconazole-desthio was not analysed for in the full scale production batches. However, this was an omission and all the batches were analysed for this compound with an LOQ of <1.0 g/kg, this impurity was not found in any of the batches above this level. This omission was corrected in addendum 12 as a corrigendum to addendum 3. This addendum has not been peer reviewed.
In addition to the above mentioned issue with the technical specification the majority of the impurities are not named correctly as they have R and S isomers and one even has diastereo isomers.

Beside the specification, the assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the identity, physical, chemical and technical properties of prothioconazole or the respective formulation. However, the following data gaps were identified:

- Method of analysis for the relevant impurity toluene in the formulations. The usual additional requirements for relevant impurities namely spectra and storage stability data where the formulation is analysed for the relevant impurity can be waived. The reason for this is that the spectra of toluene are well known and it clearly will not be formed on storage.
- Methods of analysis for the relevant impurities prothioconazole-desthio and prothioconazole–deschloro in the formulations.
- Storage stability data where the relevant impurities prothioconazole-desthio and prothioconazole–deschloro are analysed for both before and after storage.
- Spectra for the relevant impurity prothioconazole–deschloro. It is noted that there are already spectra data available for prothioconazole-desthio.

The main data regarding the identity of prothioconazole 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 prothioconazole in the technical material and in the representative formulation as well as for the determination of the respective impurities in the technical material.

Sufficient test methods and data relating to physical, chemical and technical properties and analytical methods are available to ensure that at least limited quality control measurements of the plant protection product are possible. As mentioned before methods for the relevant impurities in the product are missing.

Methods are available to monitor all compounds given in the respective residue definition for food of plant origin, water, soil and air. Residues in food of plant origin can be determined with a multi-method (The German S19 method has been validated for prothioconazole-desthio). Only single methods are available to determine residues of prothioconazole-desthio, in products of animal origin and prothioconazole, prothioconazole-desthio in soil water and air. A method is not available to monitor the glucuronide conjugate in products of animal origin. Also if the active is classified as toxic then methods for body fluids and tissues would need to be considered. All of the methods except the plant method were LC-MS/MS which are highly specific therefore negating the need for confirmatory methods. ILV data were available for the plant and animal product methods.

2. Mammalian toxicology

Prothioconazole was discussed in a meeting of experts in Parma in September 2006 (PRAPeR experts' meeting round 1).

A new specification was submitted for the large scale production. Several toxicological studies for 3 impurities (1 increased and 2 new) were submitted in the addendum to Annex C (February 2006) (see 2.8).

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

Prothioconazole is rapidly and almost completely absorbed (>90%) following oral dosing. Excretion is extensive and relatively rapid, mainly via faeces. Prothioconazole is widely distributed (mainly in the liver, followed by kidney, fat, thyroid and adrenal gland). It does not show potential for accumulation. Metabolism mainly occurs via desulphuration, oxidative hydroxylation of the phenyl moiety and conjugation with glucuronic acid. The desthio metabolite (M04) and parent prothioconazole are the main components in excreta.

2.2. Acute toxicity

Prothioconazole is of low acute toxicity via oral (LD_{50} > 6200 mg/kg bw), dermal (LD_{50} > 2000 mg/kg bw) or inhalation (LC_{50} > 4990 mg/m^3) routes. It does not show any eye and skin irritation or sensitizing potential.

2.3. Short term toxicity

Prothioconazole was tested in a number of short term toxicity studies in rats (two 4-week oral studies, 14-week by gavage, 4- week dermal), in mice (14 weeks) and in dog (13 weeks and 52 weeks).

The liver is the main target organ (increases in hepatic enzyme activity, increased liver weights and hepatocellular hypertrophy were consistent with hepatic enzyme induction). The effects in the liver were reversible after an 8 week recovery period in rats and dogs. The kidney was also identified as a target organ in rats and dogs, but not in mice (increased weights and histopathological changes, namely increased incidence and severity of basophilic tubules and tubular dilatation in rats, and interstitial fibrosis/inflammation in dogs).

The relevant short term oral NOAEL is 25 mg/kg bw/day, while the relevant dermal NOAEL after repeated exposure is >1000 mg/kg bw/day.

2.4. GENOTOXICITY

Prothioconazole gave negative results when tested in *S. typhimurium* strains and an HPRT mammalian cell mutation assay in CHL V79 cells, but gave inconsistent or equivocal results in an *in vitro* rat liver UDS assay, and induced chromosome aberrations in cultured CHL cells.

In vivo testing (a rat liver UDS assay and two mouse bone marrow micronucleus assays) showed negative results.

Overall, it can be concluded that prothioconazole is not genotoxic *in vivo*.

2.5. LONG TERM TOXICITY

In chronic studies with prothioconazole in rats and mice, the target organs were liver and kidneys. The liver effects consisted of increased weights, hypertrophy/cytoplasmic change together with enzyme induction, the latter possibly responsible of a mild alteration in thyroid hormone levels in rats, without any histopathological finding recorded.

There was no increase in neoplastic findings in the liver in either rats or mice. The incidence of neoplastic findings in the thyroids was similar between treated animals and controls.

The kidney effects (increased weights and increased severity of chronic progressive nephropathy in rats, decreased weights, tubular degeneration/regeneration and subcapsular tubular degeneration with interstitial fibrosis in mice) were also not accompanied by an increase in neoplastic findings.

The relevant chronic NOAEL is 5 mg/kg bw/day (2 year rat).

Overall, prothioconazole does not show any carcinogenic potential after repeated exposures.

2.6. REPRODUCTIVE TOXICITY

Reproductive toxicity

In a multigeneration study in rats, reproductive effects such as disruption of the oestrous cycle, increased time to insemination (not statistically significant), reduced implantation sites and increased duration of gestation (not statistically significant) occurred in parental females at high doses. These effects were accompanied by systemic toxicity and did not result in effects on mating, fertility or gestation indices. Effects on developing pups (reduced pup weight gain, reduced spleen weights and delayed preputial separation – considered secondary to reduced pup weight gain) only occurred at dose levels in which toxicity was also recorded in parental animals.

The parental NOAEL is 9.7 mg/kg bw/day, while the reproductive and offspring NOAEL is 95.6 mg/kg bw/day.
EFSA notes: a few MSs expressed their concern about the fact that the disruption of the oestrous cycle should be considered as an adverse effect relevant for classification.

Developmental toxicity
Three developmental toxicity studies were performed with rats (two by gavage and one by dermal application) and one with rabbits (gavage).
Increased incidences of microphtalmia and foetal supernumerary rudimentary ribs are evident in the first rat study at the high dose (Stahl 1997). Actually microphtalmia is observed at almost all dose rates, but significantly at the top dose level (1000 mg/kg bw/d). No dose-relationship was observed since in the mid dose the incidences are lower than in the low dose, and bilateral microphtalmia is only observed in the high dose group. A second study (Young 2004) does not show effects of microphtalmia. This indicates differences in the sensibility of the strains used.
In the second study, the increased incidence of foetal rudimentary supernumerary ribs at the high dose level (750 mg/kg bw/d) was also considered to be treatment related.
The experts agreed that these effects are adverse and dose dependent and might be linked to maternal toxicity. The maternal NOAEL is 80 mg/kg bw/d, supported by the rabbit study, based on decreased body weight gain/food consumption, functional impairments of liver and kidneys. An overall developmental NOAEL of 20 mg/kg bw/day was agreed by the experts.
Prothioconazole was proposed to be classified for reproductive toxicity as **Repro cat 3, R 63** based on the increased incidences of microphthalmia (at 1000 mg/kg, maternal toxic dose) in one out of two rat strains tested (Stahl, 1997). Some MSs expressed their concern for this effect and proposed classification as Cat 2. The meeting agreed on classification as Repro cat 3, R 63 (Repro cat 2?), to be flagged to ECB, Ispra.

2.7. NEUROTOXICITY

Prothioconazole did not show toxicity to the nervous system.

2.8. FURTHER STUDIES

Plant metabolites
Metabolites found in wheat (mainly straw) were JAU 6476-sulfonic acid (**M02**[3]), JAU 6476-alpha-hydroxy-desthio (**M18**[4]), JAU 6476- acetoxy-desthio (**M19**[5]), JAU 6476-benzylpropyldiol (**M09**[6]) and JAU 6476-triazolinone (**M03**[7]). Only M03 was also proposed in the rat metabolism.

[3] M02: JAU 6476-sulfonic acid: 1-(2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl)-1H-pyrazole-5-sulfonic acid
[4] M18: JAU 6476-alpha-hydroxy-desthio: 2-(1-chlorocyclopropyl)-1-(2-chlorophenyl)-3-(1H-1,2,4-triazol-1-yl)propane-1,2-diol
[5] M19: JAU 6476- acetoxy-desthio: 2-(1-chlorocyclopropyl)-1-(2-chlorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl acetate
[6] M09: JAU 6476-benzylpropyldiol: 2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)propane-1,2-diol

M02 was shown to have a higher acute toxicity than prothioconazole (LD_{50} 300-500 mg/kg bw); it is not mutagenic in the Ames test and does not produce any skeletal, visceral or external abnormalities at high doses (750 mg/kg bw/day), in repeated dose studies it does not show adverse effects on liver and hepatic enzymes at doses up to 163 mg/kg bw/day (90 day rat study).
M03, M09, M18 and M19 were tested for acute oral toxicity and mutagenicity *in vitro* (Ames test) showing lower acute toxicity than the parent (LD_{50} >2000 mg/kg bw) and no mutagenic potential (negative in Salmonella/microsome test).

M04[8] (JAU 6476-desthio) is the major plant metabolite of prothioconazole, as well as a rat metabolite. An extended toxicological database was presented in the DAR.
M04 is rapidly and almost completely absorbed; it is widely distributed (the highest concentrations found in liver, kidney cortex, erythrocytes and lungs). Excretion occurred predominantly in bile, and the elimination half-life and mean residence time were prolonged due to persistent enterohepatic re-circulation. It does not show potential for bioaccumulation. On the basis of a dermal absorption study in rhesus monkeys using an SC formulation containing M04, a 20% dermal absorption was considered appropriate for use in operator exposure calculations.
M04 acute oral toxicity was low, it did not show any mutagenic and carcinogenic potential. The NOAELS for the short-term studies were based on liver effects. Other effects were increased ovary weights, as a result of disturbance of hormone balance), and in one rat study, an increase number of follicles and stromal cell oedema. Although no effect was seen on ovary weights in the 13 week mouse study, there was haemorrhagic degeneration of corpora lutea.
As in the short-term studies the liver was the target organ in the chronic toxicity and carcinogenicity studies. The NOAELs for both studies were set using liver effects (histopathology and reduced weight gain). The endocrine system was also affected in rats leading to reductions in thyroid hormone (T4), ovary weights (through reduced normal ovarian atrophy with age), and histopathology in the adrenal cortex. These effects are likely to be related to enhanced endocrine hormone clearance by enzymes induced in the liver.
Effects on reproduction in rats comprised reduced litter size, reduced pup viability, pre-weaning growth retardation and some incidents of cleft palate. In the 2-generation study, a number of P and F1 generation females exhibited dystocia. P and F1 generation maternal livers showed hepatocyte vacuolation and slight to moderate liver necrosis. In the developmental studies increased incidences of cleft palate in the rat and rabbit and supernumerary 14th ribs in the rat only were observed. M04 was developmentally toxic in rats via the oral and dermal routes at non maternally toxic dose levels, and in rabbits at least via the oral route. The experts proposed the classification as cat 2, R61 (R62?) to be flagged to ECB in Ispra.

Beside the metabolites which are structurally related to the parent compound, grains and oilseeds, rotational crops and animal products are expected to contain significant amounts of the so-called

[7] M03: JAU 6476-triazolinone: 1-(2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl)-1H-1,2,4-triazol-5(4H)-one
[8] M04: JAU 6476-desthio (M04): 2-(1-chlorocycloproyl)1-(2-chlorophenyl)-3-(1,2,4-triazol-1-yl)-propan-2-ol

triazole derivative metabolites (**see 3.1.1**). During the PRAPeR expert meeting 14 on toxicology in January 2007, reference values were agreed for these metabolites (**see 2.10**).
However, information/data are missing about the comparability of the toxic mode of action of prothioconazole and the triazole metabolites and it cannot be concluded on the resulting combined toxicity.

Impurities
The presence of one increased impurity (JAU 6476-deschloro, from 0.2% to 1.5%) and two new impurities (0.5 and 0.2%) in the new technical specification for the large scale production triggered the conduct of several toxicological studies.
The two **new** impurities were not acutely toxic, not genotoxic *in vitro* and *in vivo*, and considered of similar or lesser toxicity than prothioconazole.
JAU 6476-deschloro has no acute oral toxicity in rats, is non mutagenic in an Ames test, not clastogenic *in vitro* for mammalian cells and is not mutagenic in the V79-HPRT forward mutation assay. A mouse micronucleus test *in vivo* also demonstrated the absence of clastogenicity. In a pilot study with rats, maternal and developmental toxicity were comparable with those of prothioconazole.
The two materials (pilot production and large scale production) were concluded equivalent by the experts. However, JAU 6476-deschloro was shown to be a skin sensitizer whereas prothioconazole has no sensitizing properties. EFSA raised some concern after the experts' meeting about the sensitizing potential of the new technical specification since the impurity exceeds the 1% trigger for classification and labelling. Consequently, the increased level of JAU 6476-deschloro shall be considered of toxicological relevance and give a classification R43 unless further test with the new technical specification will give evidence for no sensitizing properties (the final decision for classification and labelling will be taken by ECB).

2.9. MEDICAL DATA

No information on medical surveillance or poisoning incidents was provided.

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

Acceptable Daily Intake (ADI)
The critical studies for setting the ADI are the two year (chronic) rat study and the 1 year dog study. The NOAELs in these studies were 5 mg/kg bw/day. Applying a 100 fold assessment factor, the proposed ADI for prothioconazole is therefore 0.05 mg/kg bw/day.

Acute Reference Dose (ARfD) and Acceptable Operator Exposure Level (AOEL)
The experts proposed to base both values on the combined developmental NOAEL of 20 mg/kg bw/day applying a safety factor of 100, giving a value of 0.2 mg/kg bw.

Reference values were agreed for the metabolite M04, JAU 6476-desthio:
- ADI 0.01 mg/kg bw/d based on the rat carcinogenicity study, with a SF 100

- AOEL and ARfD 0.01 mg/kg bw/d based on the rat developmental study, with a SF 100.

Reference values agreed for the triazole metabolites :

- 1,2,4- triazole: ADI 0.02 mg/kg bw/d, based on the rat multigeneration study.
  ARfD 0.06 mg/kg bw/d, based on the rat developmental study.
- triazole acetic acid: the ADI and ARfD of 1.2.4-triazole were chosen due to the limited database available.
- triazole alanin: ADI 0.1 mg/kg bw/d, based on the rat developmental study.
  ARfD 0.1 mg/kg bw/d, based on the rat developmental study.

2.11. DERMAL ABSORPTION

No dermal absorption studies were performed and submitted with the representative formulation. Hence, the experts agreed on a default value of 100% for prothioconazole.
As for M04, a 20% dermal value has been derived from a dermal absorption study in monkeys.

2.12. EXPOSURE TO OPERATORS, WORKERS AND BYSTANDERS

The representative plant protection products for prothioconazole are an EC 250 and a FS 100 formulation, to be used on cereals (wheat, rye, triticale, barley, oat and rape) and for seed treatment, respectively. Application rate is 0.175-0.2 kg/ha for the EC product and 5-10 g/dt seed for the FS formulation.

Operator exposure

Field spraying of EC 250 on cereals

The exposure to prothioconazole for application of the EC formulation on cereals has been assessed with the German and UK POEM models.
A refinement of the calculations was performed after the experts' meeting proposal of a new AOEL (from 0.25 to 0.2 mg/kg bw/day) and presented in an addendum (Dec 2006).

Estimated exposure expressed as percentage of the AOEL (0.2 mg/kg bw/day):

Scenario	Model	No PPE	With PPE*
Mechanical spraying cereals	German model	127%	16%
	UK POEM	514%	71%

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

German model: gloves, standard protective garment and sturdy footwear during mixing/loading; standard protective garment and sturdy footwear during application.

The estimated operator exposure is below the AOEL when PPE is worn for mechanical spraying in cereals, using the UK-POEM and the German model.
In the DAR a field study performed in Germany with the EC formulation was summarised, showing exposure levels of about 2% of the AOEL. The RMS also presented an estimate of the exposure to

M04, that may be formed in diluted prothioconazole formulations, particularly on clothing, skin and plant surfaces during drying processes. The same field study described above was used to derive potential exposure to desthio prothioconazole: even accounting for 100% dermal absorption, the estimated exposure is less than 20% of the AOEL for desthio metabolite (0.01 mg/kg bw/day).

- Seed treatment with the FS 100 formulation

The exposure to operators working at the treatment of seeds with the prothioconazole FS formulation has been assessed through compound specific studies in different activities (seed treatment and loading of a drilling machine with seeds treated) for large scale uses only. The operator exposure accounts for about 55% of the AOEL for operators performing mixing/loading/calibration/cleaning and bagging. For sowing, the estimated exposure is about 4% of the AOEL.
As for the M04, the exposure for the operators is estimated to be 50% and 10% (considering 20% dermal absorption) for mixing/loading/calibration/cleaning and bagging, respectively.

Worker exposure

- Field spraying of EC 250 on cereals

The exposure to workers after spraying in cereals is mainly due to inspection activities. In the DAR it has been estimated with the use of German re-entry model (Hoernicke et al, 1998) together with published transfer coefficient data, showing exposure level of about 45% of the AOEL (new value of 0.2 mg/kg bw/day).

Considering the assumption that all prothioconazole on plants is degraded to desthio metabolite and a 20% dermal absorption, the estimated workers' exposure to desthio metabolite is about 160% of the AOEL. This assumption was considered as an unrealistic worst case, as it assumes no dissipation of dislodgeable foliar residues (DFR) due to weathering or growth from any of the treatments applied. Residue decline studies are available which were conducted in accordance with the supported GAP (spray interval of 14 – 21 days). Using these data, which suggest a conservative decline in DFR of 50% in between applications, the estimated exposure is about 96% of the AOEL .

- Seed treatment with the FS 100 formulation

No re-entry scenario is expected for seed treatment.

Bystander exposure

- Field spraying of EC 250 on cereals

Exposure estimates for bystanders during prothioconazole spraying on cereals represent about 1% of the AOEL of 0.2 mg/kg bw/day. Even for desthio metabolite, the estimated exposure is negligible.

- Seed treatment with the FS 100 formulation

Bystander exposure during seed treatment is unlikely to take place. No assessment needed.

3. Residues

Prothioconazole was discussed at PRAPER experts' meeting for residues (PRAPER 05) in September 2006.

3.1. NATURE AND MAGNITUDE OF RESIDUES IN PLANT

3.1.1. PRIMARY CROPS

The metabolism of prothioconazole has been investigated in wheat after foliar application and seed treatment and in peanut after foliar treatment. The design of the studies was in accordance with the representative uses supported by the manufacturer. In both crops the residue extractability is high. Prothioconazole is extensively metabolised. In a first step the sulphur group of the triazolinethione ring is oxydised to the corresponding sulfonic acid. Subsequent elimination of the sulfonic acid moiety results in prothioconazole-desthio (metabolite M04) which is consistently the major prothioconazole-structurally related metabolite in all plant parts and for all growth stages, except in nutmeat, where it was not found. This metabolite is further hydroxylated in the chlorophenlyl ring forming various hydroxyl-desthio isomers and dihydroxy-olefins. Similarly, α-hydroxylation of prothioconazole-desthio was also observed. A dimerisation product and other metabolites resulting from combined oxidation of the sulphur atom and hydroxylation of the chlorophenyl ring were also identified. Cleavage of the triazole moiety is also observed resulting in the 'triazole derivative metabolites' which consist essentially in triazole alanine and triazole acetic acid. These compounds are common, unspecific metabolites of triazole fungicides. Triazole alanine and triazole acetic acid are massively translocated to wheat grains where they represent 90% of the Total Radioactive Residues (TRR). Although the metabolism study in peanut did not use radiolabelling in the triazole ring, it is expected from studies carried out with other triazole fungicides that these triazole derivative metabolites are also present as major constituent of the residue in oilseeds.

The residue definition proposed for monitoring is prothioconazole-desthio. The need for monitoring the parent compound was not considered necessary by the expert meeting as its toxicity and its occurrence in plants are lower.

The residue definition for risk assessment was discussed by the expert meeting. Many metabolites are structurally closely related to prothioconazole-desthio and consist mainly in hydroxylated forms of this compound. Their individual level is generally low, but their total amount suggests that they may have a significant contribution to the toxicological burden the consumer is exposed to. The applicant submitted a position paper supporting the view that these metabolites due to their structure were assumed to have a toxicological profile similar to that of parent compound and prothioconazole-desthio. DEREK analysis did not show any additional alerting toxicological properties. The expert meeting on toxicology was not in a position to evaluate this information and to draw a conclusion. It was therefore assumed by the expert meeting on residues as worst case that the toxicological end points allocated to prothioconazole-desthio should also be applied to these metabolites and it was agreed to include in the residue definition for risk assessment all metabolites containing the 2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl-2H-1,2,4-triazole moiety, their sum being expressed as prothioconazole-desthio. The information on the metabolic pattern in primary crops after

seed treatment or foliar spray, as well as in rotational crop is rather consistent and allows establishing conversion factors of 2 for cereal grain and of 3 for cereal and rapeseed straw respectively. For rapeseed, it was considered appropriate to use the same factor as for cereal grains as no conversion factor could be set for oilseeds from the metabolism study in peanut.

As far as the triazole derivative metabolites are concerned, a memorandum[9] was recently issued by the Office of Pesticide Program of the US EPA, in which an aggregate human risk assessment was conducted for 1,2,4-triazole and its alanine and acetic acid conjugates. These metabolites appear to exhibit toxic effects, in particular on the development and EPA allocated them reference values. Similarly, several Member states (UK, Ireland, Belgium, Sweden, Denmark, Italy) carried out an assessment of the toxicological properties of the triazole derivative metabolites in the framework of the peer review of some active substances belonging to the triazole chemical class. All these assessments were critically considered during the PRAPeR expert meeting 14 on toxicology in January 2007 and toxicological end points and reference values were agreed. Based on this it was also agreed by the PRAPeR expert meeting 15 on residues in January 2007 that a consumer risk assessment should be conducted.

Therefore the currently proposed residue definition for risk assessment will need to be reconsidered for inclusion of the triazole derivative metabolites, and its final drafting will depend on whether their effects are expected to act in combination or not and on their relative potency.

A sufficient number of supervised residue trials have been submitted in accordance with the representative uses supported by the notifier. In these trials, prothioconazole-desthio residues were determined consistently with the residue definition for monitoring.

For seed treatment in cereals 8 trials in wheat (4 in Northern Europe and 4 in Southern Europe) demonstrate that residues in grains are below the Limit Of Quantification (LOQ) in grains and straw (0.01 and 0.05 mg/kg respectively). This no-residue situation is further supported by 14 additional trials in wheat and barley carried out in both European regions where immature plants were sampled and consistently contained residues below a LOQ of 0.05 mg/kg.

For foliar treatments in cereals, 11 trials in Northern Europe and 8 trials in Southern Europe showed no residues at harvest in wheat grains (below the LOQ of 0.01 mg/kg). In barley grains, 9 trials are available for Northern Europe all resulting in residues below the LOQ of 0.01 mg/kg. Eight trials were submitted supporting the use in barley in Southern region and showed measurable residues in some instances, but not exceeding 0.02 mg/kg. A lot of information is available for residues in straw in both Northern and Southern regions, ranging from 0.08 to 1.1 mg/kg at normal harvest time.

In addition, the applicant submitted a statement in March 06, reporting results of 16 additional residue trials (10 in wheat and 6 in barley) conducted in 2005 supporting the foliar use of prothioconazole. In these trials, not only prothioconazole-desthio but also parent prothioconazole were analysed. In all trials residues of parent compound were below the LOQ on whole plant, while levels of prothioconazole-desthio were ranging from below the LOQ to 0.85 mg/kg. These data were not peer-

[9] 1,2,4-triazole, Triazole Alanine, Triazole Acetic Acid: Human Health Aggregate Risk Assessment in support of Reregistration and Registration Actions for Triazole-derivative Fungicide Compounds. 7 February 2006. DP Number 322215.

reviewed due to the late submission but support the non inclusion of the parent compound in the residue definition for monitoring.

In rape, 12 valid trials were performed (8 for Northern region and 4 for Southern region). Residues in seeds were low, ranging from below the LOQ of 0.01 mg/kg to 0.02 mg/kg. The Highest Residue level (HR) found in rape straw was 0.20 mg/kg.

These results can be considered as reliable on the basis of storage stability studies demonstrating that residues of prothioconazole and its metabolite prothioconazole-desthio are stable in wheat matrices under deep-freeze conditions for periods of 60-180 and 540 days respectively. A weak storage stability for long term storage (periods exceeding 180 days) was noted for the parent compound but this does not alter the validity of the residue trials given its low contribution to the total residue.

As residues in treated commodities at harvest are at or near the LOQ, and given the low degree of ADI exhaustion in consumer risk assessment, the effect of processing on the nature and level of residues were not investigated.

Field trials regarding the triazole derivative metabolites are not available.

3.1.2. SUCCEEDING AND ROTATIONAL CROPS

In succeeding crops, the residue pattern is similar to that observed in primary crops. The residue definitions proposed for primary crops are evenly valid. Under the experimental conditions of the submitted confined rotational crop study, residues of prothioconazole-desthio were present in edible part of Swiss chard and turnip at the level of 0.01 mg/kg, when these plants were sowed 28 and 146 days after application of the highest possible annual dose of prothioconazole on bare soil. The total amount of all metabolites containing the prothioconazole-desthio common structural moiety was around 0.03 mg/kg for the same time intervals. Therefore, under practical conditions of use of prothioconazole according to the representative uses and considering that a fraction of the applied rate is intercepted by the cereal crop, no residue of any metabolite above 0.01 mg/kg is expected in rotational crops and no plant back restriction needs to be proposed.

No information is available as far as the uptake of triazole derivative metabolites by rotational crops is concerned, given that no study was conducted with radiolabelling in the triazole ring.

3.2. NATURE AND MAGNITUDE OF RESIDUES IN LIVESTOCK

A goat metabolism study indicated that prothioconazole is rapidly adsorbed and largely excreted. It was found unchanged in all tissues in amounts varying from 1 % (milk) and 18 % (kidney) of the TRR. About 10 metabolites were identified, suggesting a similar metabolic pathway to that observed in rats. However as animals are more likely to be exposed to the prothioconazole-desthio metabolite, the metabolism of this compound was also investigated. Its metabolic pathway consists in various types of hydroxylation affecting the chlorophenyl ring leading to metabolites existing in free form or as glucuronide or sulphate conjugates. Prothioconazole-desthio is found as major constituent of the TRR in liver (31 % of the TRR), fat (14 % of the TRR), in lesser amount in muscle (2 % of the TRR) and kidney (7 % of the TRR), and was not found in milk. Its glucuronide conjugate was found in milk (6 % of the TRR) and in higher amounts in kidney (24 % of the TRR). About 10 different compounds were in total identified of which metabolite JAU 6476-desthio-3,4-dihydroxy-diene (M32) as free or

glucuronide conjugate forms was the most abundant (10%, 6%, 32%, 23% and 27 % of the TRR in milk, liver, muscle, kidney and fat respectively). Due to the labelling position in the metabolism study, no information is available concerning the triazole derivative metabolites. Nevertheless, based on information available for active substances from the same chemical class, it may be expected that these metabolites are formed in livestock.

The proposed residue definition for monitoring in animal products is the sum of prothioconazole-desthio and its glucuronide conjugate, expressed as prothioconazole-desthio. The need for including the glucuronide conjugate in the residue definition results from the fact that the free metabolite was not found in milk and cannot therefore act as a valid marker compound.

Given the complex metabolic pattern in livestock, and similarly to plant products, the residue definition proposed for risk assessment in animal commodities is the sum of prothioconazole-desthio and all metabolites containing the 2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl-2H-1,2,4-triazole moiety expressed as prothioconazole-desthio. As for plant commodities, conversion factors between residue definition for monitoring and for risk assessment were established.

Using the appropriate conversion factors for feedingstuffs, the RMS calculated the potential exposure of livestock to all prothioconazole metabolites containing the common moiety, in accordance with the residue definition for risk assessment. These calculations used Supervised Trials Median Residue (STMR) values for prothioconazole-desthio in feed commodities instead of Highest Residue (HR) values. This approach is controversial for MRL setting as it may be considered that animals may be fed with straw coming from a same field for several consecutive weeks. Using the RMS approach, and considering the result of the submitted feeding study in lactating caw, measurable prothioconazole-desthio residues of about 0.01 mg/kg are expected only in liver of ruminant. In other tissues, no residue of this compound is expected above the respective analytical LOQs (0.01* mg/kg in kidneys, meat and fat and 0.004* mg/kg in milk).

Livestock feeding studies aimed to determine the levels of triazole derivative metabolites in animal commodities are not available. For the conduction of such studies, account should be taken of the practical ratio between prothioconazole related metabolites and the triazole derivative metabolites in the animal diet in order to define the appropriate animal exposure regimes.

3.3. CONSUMER RISK ASSESSMENT

Provisionally, no risk for the consumer resulting from the use of prothioconazole according to the representative uses in cereals and rapeseed is expected.

This provisional conclusion is drawn under restriction of the exposure and risk assessments, related to the triazole derivative metabolites, which still need to be carried out, considering their possible presence in cereal grains, rotational crops and animal products. Data allowing a reliable assessment of the consumer exposure through those commodities are lacking.

For both chronic and acute risk assessments, toxicological end points and reference values of prothioconazole-desthio were used.

Chronic and acute exposure assessments were carried out in accordance with the current WHO guidelines.

Chronic exposure

Theoretical Maximum Daily Intake (TMDI) calculations were made using the WHO typical European diet for adult consumers. Residues in cereals, rape seeds and in animal commodities were considered to be at the level of the respective proposed MRLs, and appropriate conversion factors for risk assessment for each plant or animal commodity were used. The resulting calculated TMDI amounted to 6 % of the ADI.

A National Estimated Daily Intake (NEDI) assessment was also conducted according to consumption patterns in UK for 10 population subgroups, including infants, toddlers and children. These consumption patterns take into consideration possible high individual consumption levels. Residues in cereals and rape seeds were considered to be at the level of the respective STMRs. Residues in animal commodities were determined from the results of feeding studies using a linear regression for the 1N animal exposure rate. Appropriate conversion factors for risk assessment for each plant or animal commodity were applied. Based on these assumptions, the calculated NEDIs were equal or below 3 % of the ADI in all 10 populations of UK consumers.

Acute exposure

National Estimates of Short Term Intakes (NESTI) were carried out on the basis of UK national consumption data. Residues in cereals, rape seeds and animal products were considered to be at the level of the respective proposed MRLs, and appropriate conversion factors for risk assessment were used. Exposure of the adult population only is relevant for the hazard related to the ARfD (developmental effects). Based on this, all calculated NESTIs were equal or below 5 % the ARfD in the adult population.

3.4. PROPOSED MRLS

Based on the available supervised residue trials and animal feeding studies, the following MRLs can be proposed:

Prothioconazole-desthio:

Commodity	***Proposed MRL (mg/kg)***
Wheat, rye, triticale	0.01*
Barley, oats	0.05
Rape seed	0.05

* Indicates that the MRL is set at the LOQ

Sum of prothioconazole-desthio and its glucuronide conjugate, expressed as prothioconazole-desthio:

Commodity	***Proposed MRL (mg/kg)***
Liver of ruminants	0.01
Meat, milk, fat and kidney of ruminants	0.01*

* Indicates that the MRL is set at the LOQ

It is reminded that the MRLs for animal products are proposed assuming STMR levels in feedingstuff. Considering HR levels potentially present in feed items, MRL proposals for ruminant liver and kidney should be changed to 0.02 and 0.01 mg/kg respectively. This would not alter the conclusion of the risk assessment.

4. Environmental fate and behaviour

The fate and behaviour in the environment of prothioconazole was discussed in the meeting of experts (PRAPeR 02) of September 2006 on basis of the addendum to the DAR (October 2005).

4.1. FATE AND BEHAVIOUR IN SOIL

4.1.1. ROUTE OF DEGRADATION IN SOIL

The aerobic route of degradation of phenyl-UL-^{14}C and 3,5-triazole-^{14}C labelled prothioconazole was investigated in four different soils at 20 ºC and 48-49% maximum water holding capacity (MWHC) under dark conditions. The soils covered a range of pH values (5.9-7.2), clay contents (5.0-39.6%) and organic carbon contents (0.79-2.14%).

The proposed metabolic pathway of prothioconazole in soil is dominated by reactions at the sulphur atom of the triazole ring, e.g. oxidation, methylation, loss of sulphur or exchange of sulphur against oxygen. Prothioconazole is converted extensively (maximum 49.4% AR in the triazole-label, day 7) to its desthio metabolite (**prothioconazole-desthio**, M04) and, to a lesser extent, to another major metabolite named **prothioconazole-S-methyl** (M01[10]), which was detected with maximum level of 14.6% AR at 7 days (triazole-label). The predominant portion of degradation products found within these studies contained both the phenyl and the triazole ring. No other major metabolites were detected, although a total of eight minor degradation products were detected in both studies at levels <5.5% AR. The degradation of prothioconazole is characterized by a low mineralization to CO_2 (0.3-10.7% AR) and a relatively high incorporation as non-extractable residues (35.6 - 48.3% AR at 120 days). No attempts were made to investigate the nature of bound residues.

Degradation was not tested at lower temperatures (10 ºC).

Two additional laboratory studies were performed to investigate the aerobic degradation of the major metabolites prothioconazole-S-methyl (M01) and prothioconazole-desthio (M04), under dark conditions at 20 ºC with four soils. By the end of the study (125 and 120 days) the maximum levels of M01 and M04 detected were in the range 2.5%-18.6% AR and 2.3%-20.4% AR, respectively. Degradation of M01 and M04 produces other minor metabolites and ultimately bound residues (maximum 43.3% AR after 125 days for M01 and maximum 44.7% AR after 90 days for M04) and CO_2 (maximum 53.7% AR after 125 days for M01 and maximum 62.1% AR after 120 days for M04).

[10] M01: prothioconazole-S-methyl or JAU 6476-S-methyl = 2-(1-chlorocyclopropyl)-1-(2-chlorophenyl)-3-(4,5-dihydro-5-methylthio-1,2,4-triazolyl-1)-propan-2-ol

Soil degradation under anaerobic conditions was not investigated, but as a seed treatment formulation is also being considered, an anaerobic aquatic metabolism study was submitted. Results indicated a relatively rapid breakdown of parent to M01, which seemed to accumulate. However, it was considered that, under the representative uses proposed, prothioconazole will not be exposed to anaerobic conditions and, therefore, it is unlikely there would be significant formation of M01 under field anaerobic conditions.

A soil photolysis study is available with phenyl-^{14}C-labelled prothioconazole. Results demonstrated prothioconazole to be degraded rapidly (prothioconazole amounted to 18.6% AR in the irradiated samples after 15 days, end of the study) on soil surface if irradiated by simulated sunlight. However, the fast degradation observed for the dark control (19.0% AR at 15d) revealed phototransformation not to be the dominant process of degradation. M04 appears at relatively high concentrations in both irradiated and dark control samples (maximum observed at day 7: 38.5% A.R. and 29.4% A.R respectively), indicating that photolysis will not significantly contribute to the overall degradation of prothioconazole in soil under environmental conditions. The first order DT_{50} value for the degradation of the active ingredient yielded 4.1 days, equated to 22.9 days under sola summer conditions of Athens (Greece) in June.

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

Degradation rates of prothioconazole and its metabolites prothioconazole-S-methyl (M01) and prothioconazole-desthio (M04) were investigated in the same degradation studies used to establish the route of degradation. Prothioconazole is of very low persistence in soil (DT_{50}lab at 20 ºC = 0.07 to 1.27 days), whereas metabolite M04 and M01 are of low to moderate persistence (DT_{50} = 7-34 days and 5.9-46.0 days, respectively). The metabolite 1,2,4-triazole did not exceed 2% of applied radioactivity in soil metabolism studies and therefore no further assessment was required. Following the discussion on the triazole derivate metabolites (PRAPeR experts' meeting 12 on fate and behaviour), an agreed list of end points for 1,2,4-triazole was compiled and the available first order DT_{50} values in soil ranged from 5.0 days to 9.9 days (n = 3) at 20 ºC and pF2.

Field dissipation of prothioconazole has been investigated in eight studies at different sites in northern Europe (Germany, Great Britain and France) and southern Europe (France, Italy). Four of the sites were not cropped and the remaining four were sown with spring barley just prior to the application of the test substance directly to the soil surface. Analyses from each site were conducted on samples from depths up to 50cm. Soil residues were restricted to the top 10cm soil horizon. Neither prothioconazole nor the two metabolites M01 and M04 were detected below this soil layer at any sampling interval in any study. The maximum levels of prothioconazole detected in the 0-10 cm soil layer were in the range 35.5-70.3 µg/kg.

Since the metabolite M01 was not detected above the LOQ in any study, the RMS did not consider prothioconazole-S-methyl to be a major metabolite under field conditions. The need for predicted environmental concentration (PEC) in soil for this metabolite was discussed in a meeting of experts (PRAPeR 02). It was agreed that even if the detection limit in the field studies did pick up the

metabolite at levels below the LOQ (6 µg/kg), the LOQ (2 µg/kg) was only about 10% relative to the initial concentration of prothioconazole in the field studies. Therefore, it was concluded that the analytical method was not appropriate to measure M01 concentrations in the field studies, and consequently, an exposure assessment for M01 was required.
The maximum levels of the metabolite prothioconazole-desthio in the top 10cm horizon were in the range 30.4 – 67.8 µg/kg.
The first order half-lives obtained from the field studies were 1.3-2.8 days for prothioconazole, and 16.3-72.3 days for M04.

PECsoil values were recalculated by the RMS for the active substance and for prothioconazole-desthio (M04). In order to address the possibility that the prothioconazole seed treatment could be applied to the same crop as the foliar treatment, the calculations performed by RMS assumed application of the seed treatment at drilling followed by three foliar applications of 200 g a.s./ha at 14 day intervals in the spring (182 days after drilling). It should be noted that the seed drilling rate assumed by the RMS was higher than that used as the basis for the GAP (230 kg seed/ha compared to 180 kg seed/ha, equivalent to 30 g a.s./ha in place of the proposed maximum use rate of about 18 g a.s./ha). Calculated values were based on highest DT_{50} values from the field studies. The use of the 90th percentile DT_{50} derived from field trials proposed by the applicant to calculate PECsoil for the metabolite M04 was discussed in the meeting of MS experts. It was noted that the use of the worst case value from field studies is a standard approach, justified by the fact that the DT_{50} values derived from a relatively small number of field sites are used to address the risk to the large range of field and soil types distributed across Europe. Therefore the use of the 90th percentile value was not considered appropriate in this case. The maximum PECsoil values for prothioconazole and metabolite M04 were 0.133 mg/kg and 0.143 mg/kg, respectively.
In the original DAR no calculation was performed for the metabolite prothioconazole-S-methyl, with the justification that this metabolite was not detected above the LOQ in any of the eight field studies. However, at the meeting of experts the RMS was asked to calculate PECsoil for this metabolite (see above) using the degradation rate derived from the laboratory study (highest first order DT_{50} = 46 days). The same assumption used for the parent and M04 estimations regarding the application rate (seed treatment in combination with the use as spray application) was made. The exposure assessment for M01 in soil (maximum PEC is 0.037 mg/kg) was presented in an addendum dated December 2006[11] and therefore was not peer reviewed; however, the EFSA agrees with the PECsoil values provided.

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

Adsorption coefficient for prothioconazole could not be determined via standard batch equilibrium studies due to the instability of the compound in these systems. Therefore, the distribution of prothioconazole in an aged column leaching study was used to estimate Kd and K_{oc} values. Phenyl-

[11] Addendum 11 to the Report and Proposed Decision of the United Kingdom made to the European Commission under Article 8(1) of 91/414/EEC – Risk assessment for the soil metabolite prothioconazole-S-methyl (M01).

UL-^{14}C radiolabelled prothioconazole was applied on a loamy sand soil and incubated at 20ºC under aerobic conditions for 30 hours. The resulting values for prothioconazole were Kd = 15.2 and K_{oc} = 1765 mL/g (slightly mobile compound). At the end of the study, the extracted radioactivity was composed of 22.7% unchanged parent compound, the known metabolites from the soil metabolism study M04 (31.8% AR), M01 (8.1% AR) and prothioconazole-sulfonic acid (M02) (1.5%). The total radioactivity in the leachate accounted for only 1.1% AR of the applied radioactivity, and in the leachate fraction a radioactivity content of < 0.2% of the applied radioactivity was measured.

The leaching behaviour of phenyl-UL-^{14}C radiolabelled prothioconazole was further investigated in a non-aged soil column leaching study on four soils. The level of radioactivity detected in the leachates was < 1% AR in all samples. Therefore, the leachate fractions were not analysed. The majority of the residue of the active substance was detected in the top 6 cm layer (14.6-40.7% AR in 0-6 cm layer, not detected in the 6-12 cm layer), this also being the case for the metabolites prothioconazole-S-methyl (5.5-11.2% AR in the 0-6 cm layer, not detected in the 6-12 cm layer) and prothioconazole-desthio (15.4-28.0% AR in the 0-6 cm layer, not detected in the 6-12 cm layer).

Adsorption/desorption of prothioconazole -S-methyl (M01) and prothioconazole–desthio (M04) were investigated by batch equilibrium experiments in four soils. The calculated adsorption K_{oc} for M01 was in the range 1973.6 – 2995.0 mL/g, and for M04, the calculated adsorption K_{oc} was in the range 523.0 – 625.3 mL/g (slightly mobile). Based on the agreed (PRAPeR experts'' meeting 12) list of end points for 1,2,4-triazole, the K_{foc} values for this minor soil metabolite of prothioconazole are in the range of 43-202 mL/g (n=4).

4.2. FATE AND BEHAVIOUR IN WATER

4.2.1. SURFACE WATER AND SEDIMENT

In sterile water at 50ºC prothioconazole was stable at pH 7 and 9. Only at pH 4 a slight hydrolytic degradation of prothioconazole was observed after 168 hours of incubation (93.3% AR). The DT_{50} of prothioconazole at 25ºC was estimated by extrapolation of the 50ºC data and was found to be more than one year at any environmental pH.

The phototransformation of prothioconazole and its degradates in water was studied within several laboratory studies. In an aqueous photolysis study at pH 7, prothioconazole-desthio M04 (55.7% AR, after 11 days), **prothioconazole-thiazocine**[12] M12 (14.1% AR, after 5 days) and **1,2,4 triazole** M13 (11.9% AR, after 18 days) were detected as being major metabolites. The mean experimental half life for prothioconazole was 47.7 hours, corresponding to a predicted environmental half-life under June solar summer conditions of 7.1 days in Phoenix, Arizona, USA and 11 days in Athens, Greece.

[12] M12 = prothioconazole-thiazocine or M12 = 6-(1-chlorocyclopropyl)-6,7-dihydro-5*H*-[1,2,4]triazolo[5,1-b][1,3]benzothiazocin-6-ol

Using the UV absorption data and the respective degradation kinetics, mean quantum yields for prothioconazole were calculated. Based on the study results, direct photodegradation in aqueous solution maybe expected to contribute to the elimination of prothioconazole in the environment.
A corresponding study with the major metabolite M04 indicated that a contribution of the direct photodegradation in water to the overall elimination of M04 in the environment is not to be expected.
The expected maximum amount of prothioconazole-thiazocine (M12) in surface water was estimated on the basis on information from the photolysis and water-sediment studies. It was concluded that, under environmental conditions, this metabolite is unlikely to be formed at >10% in natural surface water systems.
The molar extinction coefficient of the metabolite 1,2,4-triazole (M13) was investigated. Since M13 does not absorb UV light above 290nm, aqueous photolysis of this metabolite is not expected.
Studies on readily biodegradability were not submitted.

The behaviour of prothioconazole in two different water/sediment systems was investigated under aerobic conditions in the dark at 20ºC. Two radiolabelled compounds, [phenyl-UL-^{14}C] and [3,5-triazole-^{14}C] prothioconazole were used as test substances. A proportion of the active substance partitioned quite rapidly into the sediment, with maximum levels of prothioconazole reaching 22.6% to 23.4% AR in the sediment on day 1 and decreased at the study end (3.3-6.8% AR and 3.4-9.5% AR after 121 days). The amount of the unextracted residues increased significantly during the course of the study. More than 12 metabolites were formed and five of them were identified. Major metabolites in water were prothioconazole-desthio M04 (maximum = 32.3% AR by day 7) and 1,2,4-triazole M13 (maximum = 37.2% AR by day 121). The high levels of metabolite M13 were observed in only one of the systems. In the sediment extracts, M04 was the only major metabolite (maximum = 26.9% AR by day 14).
Prothioconazole dissipated rapidly in both systems, and the DT_{50} values for the water phase were calculated using first order kinetics (DT_{50} water = 0.8 – 1.0 day). Bi-phasic kinetics (“Hockey Stick”) were applied to evaluate the entire water/sediment system (DT_{50} whole system = 1.6 – 2.8 days).

A water/sediment study under anaerobic conditions is available. The amounts of $^{14}CO_2$ and organic volatile radioactive substances were very low (< 0.1% AR throughout the study). The DT_{50} values of prothioconazole were calculated to be 2.5 days for the water layer and 72 days for the entire system, and followed first–order reaction kinetics. Prothioconazole-S-methyl (M01) was identified as major metabolite in the sediment (maximum 77.0% AR by day 240).

Predicted Environmental Concentrations in surface water (PECsw) were calculated for prothioconazole and relevant metabolites prothioconazole desthio (M04) and 1,2,4-triazole (M13). The maximum DT_{50} value (1.0 days) for the active substance in the water phase of the aerobic water/sediment study was used. No DT_{50} values were available for the metabolites and therefore no degradation was assumed. Conversion rates of 32.3% (M04) and 37.2% (M13) derived from the water/sediment study were used in max PECsw calculations for the metabolites, with correction for molecular weight. As the dossier was submitted before FOCUS Surface Water Report became

available, calculations were performed in line with the EC Guidance document "Guidance Document on Aquatic Ecotoxicology" (Sanco/3268/2001). Values have been calculated considering only spray drift as the main entry route to surface water, based on a 90th percentile spray drift value for a single application or 77th percentile spray drift value for three repeated applications at 14 day intervals. The MS experts (PRAPeR 02) agreed that the approach taken by the applicant is acceptable. Drainage and runoff routes of exposure to surface water bodies should be taken into account by MS when these entry routes are relevant and the pertinent risk assessments to aquatic organisms should be completed for prothioconazole and its metabolites. A supplementary study on the possible aquatic environmental exposure from the proposed use resulting from drainflow in UK was submitted and presented in the DAR. The applicant also submitted a number of papers setting out calculations of PECsw and PECsed using the German and the French models, but they were not evaluated by the RMS.

Because no DT_{50} were available for prothioconazole and prothioconazole-desthio in sediment, worst case PECsed values from spray drift were calculated assuming no degradation between foliar applications. In addition, a pseudo-PECsw for the active substance for use in the sediment dwelling organisms risk assessment was calculated assuming 77th percentile spray drift values (2.01% drift at 1 m distance) with all three foliar application assumed to be applied simultaneously.

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

The leaching behaviour of prothioconazole and the metabolites prothioconazole-S-methyl (M01) and prothioconazole-desthio (M04) have been simulated with the FOCUS-PELMO model in nine European scenarios. In order to address the maximum intended seasonal application of prothioconazole, its proposed use as a seed treatment was modelled in combination with the proposed foliar use. Winter cereals were assumed to be cultivated every year without crop rotation. The results of the modelling indicated that the proposed used of prothioconazole are unlikely to result in contamination of groundwater at > 0.1µg/L. The input parameters for the modelling were discussed at the meeting of experts. It was agreed that although a worst case value of 0 for Koc, in place of the value (= 1765 mL/g) based on aged soil column leaching study, should have been used, in the case of prothioconazole it has no impact on the assessment. It was also noted that the field DT_{50} values for the metabolites M01 and M04 were not normalised to moisture content of the soil. However, the margins against the trigger are large enough to conclude that this will have no impact on the regulatory decision.

4.3. FATE AND BEHAVIOUR IN AIR

Based on the results concerning vapour pressure (<< 4 x 10^{-7} Pa at 20ºC) and the Henry Law constant (<< 3 x 10^{-5} Pa x m^3 mol^{-1}), it can be concluded that significant volatilisation of prothioconazole is not to be expected. If low portions of the substance may reach the air in form of aerosols formed during spraying (spray drift), the chemical lifetime of prothioconazole in the troposphere was calculated to be 1.6 hours. Therefore, an accumulation of prothioconazole in the air and contamination by wet or dry deposition are not to be expected.

A longer estimated half-life of 23 hours was estimated for the metabolite prothioconazole-desthio (M04). However, the laboratory route and rate soil studies indicated that volatilisation of M04 is unlikely to take place because no volatiles were detected at levels above 0.1% AR.

5. Ecotoxicology

Prothioconazole was discussed in the PRAPeR Expert Meeting for ecotoxicology (PRAPeR 03) in September 2006.

5.1. RISK TO TERRESTRIAL VERTEBRATES

The representative evaluated uses of prothioconazole are as a fungicide with foliar application in cereal and oilseed rape (formulation JAU 6476 EC 250) and as a seed treatment in cereals (formulation JAU 6476 FS100). The RMS conducted the first tier risk assessment for generic species based on EPPO 1992 Vertebrate Scheme assuming a total dose of 0.6 kg a.s./ha applied as a single application for herbivorous vertebrates in cereals and a single dose of 0.35 kg a.s./ha in oilseed rape. No residue decline was assumed between applications. A single application of 0.2 kg a.s./ha was assumed for insectivorous vertebrates.

Birds

An overview of the risk assessment for birds is given in the tables below. The risk to birds from the use in oilseed rape is covered by the assessment for cereals.

Summary of the risk assessment for birds exposed to prothioconazole

Active substance: Prothioconazole	1st tier TER*	Proposed refinements	Conclusion of peer review
JAU 6476 EC 250 cereals			
Acute risk	LHB: >124 IB: >480	Not necessary	Low acute risk
Short-term risk	LHB: >74 IB: >862	Not necessary	Low short-term risk
Long- term/ reproductive risk	LHB: 10.4 IB: NA	Not necessary	Low long-term risk (TER=12.9 for IB calculated by EFSA in accordance with SANCO/4145/2000)
JAU 6476 FS 100 Cereal seed treatment			
Acute risk	SGB: >44	Not necessary	Low acute risk
Short-term risk	SGB: >33	Not necessary	Low short-term risk

Active substance: Prothioconazole	1st tier TER*	Proposed refinements	Conclusion of peer review
Long-term risk	SGB: **4.6**	RMS proposed no refinement necessary due to rapid decline of residues and short germination period. Risk mitigation labelling phrases to reduce exposure to treated seeds on soil surface were proposed	TER=**1.37** calculated by EFSA in accordance with SANCO/4145/2000) Further data/information to address the risk was considered necessary by the PRAPeR 03 expert meeting.

LHB: Large herbivorous bird; IB: Insectivorous bird; SGB: Small granivorous bird; NA: Not assessed

* Based on EPPO Vertebrate scheme

EFSA calculated TER values according to the Guidance document on Risk Assessment for Birds and Mammals (SANCO/4145/2000 and values above the Annex VI trigger were obtained for all time scales for the use of JAU 6476 EC 250 in cereals and oilseed rape. For the use of JAU 6476 FS 100 as seed treatment a TER of 1.37 was derived, indicating that further consideration of the long-term risk is required.

Prothioconazole-desthio was considered to be the only major metabolite in cereal foliage and acute, dietary and chronic toxicity studies were available to assess the risk. A total conversion of prothioconazole to the desthio metabolite was assumed in the assessment. The acute and short term risk to insectivorous birds is covered by the assessment for herbivorous birds.

Summary of the risk assessment for birds exposed to prothioconazole-desthio

Active substance: Prothioconazole-desthio	1st tier TER*	Proposed refinements	Conclusion of peer review
JAU 6476 EC 250 cereals			
Acute risk	LHB: >121	Not necessary	Low acute risk
Short-term risk	LHB: >61	Not necessary	Low short-term risk
Long- term/ reproductive risk	LHB: **2.5** IB: 29.8	Measured maximum residues in wheat of 3.7 mg/kg) and a mean DT_{50} of 3.2 days. TER calculated according to SANCO/4145/2000	Low long-term risk Refined TER= 27.8
JAU 6476 EC 250 oilseed rape			
Acute risk	Covered by cereal assessment	Not necessary	Low acute risk

Active substance: Prothioconazole-desthio	1st tier TER*	Proposed refinements	Conclusion of peer review
Short-term risk	Covered by cereal assessment	Not necessary	Low short-term risk
Long-term risk	LHB: 15.9	Not necessary	Low long-term risk
JAU 6476 FS 100 Cereal seed treatment			
Acute risk	SGB: >279	Not necessary	Low acute risk
Short-term risk	SGB: >163	Not necessary	Low short-term risk TER=5.2 calculated by EFSA in accordance with SANCO/4145/2000
Long-term risk	SGB: 6.9 (based on measured residue)	Maximum mean daily level on treated seed remaining on soil surface averaged over 0 to 9 day exposure and normalised to a use rate of 15 g a.s./100 kg seed (3 field trials)	TER=**1.6** calculated by EFSA in accordance with SANCO/4145/2000 Further data/information to address the risk was considered necessary by the PRAPeR 03 expert meeting.

LHB: Large herbivorous bird; IB: Insectivorous bird; SGB: Small granivorous bird; NA: Not assessed

* Based on EPPO Vertebrate scheme

The long-term risk assessment for herbivorous birds was refined by using measured residue levels of prothioconazole-desthio in green parts of cereals and a mean DT_{50} calculated from 8 trials. This resulted in TERlt above the Annex VI trigger and indicates that the risk to herbivorous birds is low.

Mammals

An overview of the risk assessment for mammals is given in the table below. The risk to herbivorous mammals in oilseed rape is covered by the assessment for cereals.

Summary of the risk assessment for mammals exposed to prothioconazole

Active substance: Prothioconazole	1st tier TER*	Proposed refinements	Conclusion of peer review
JAU 6476 EC 250 cereals			
Acute risk	SHM: >128 IM: >16000	Not necessary	Low acute risk

Active substance: Prothioconazole	1st tier TER*	Proposed refinements	Conclusion of peer review
Long- term/ reproductive risk	SHM: 11.9 IM:148	Not necessary	Low long-term risk (TER = 5.7 for LHM calculated by EFSA using the $NOEL_{repro}$ of 95.6 mg/kg bw/day in accordance with SANCO/4145/2000)
JAU 6476 FS 100 Cereal seed treatment			
Acute risk	SGM: >137	Not necessary	Low acute risk
Long-term risk	SGM: 5.3	No refinements proposed	TER = **2.77** calculated by EFSA using the $NOEL_{repro}$ of 95.6 mg/kg bw/day in accordance with SANCO/4145/2000) Further data/information to address the risk was considered necessary by the PRAPeR 03 expert meeting.

SHM: Small herbivorous mammal; IM: Insectivorous mammal; SGM: Small granivorous mammal;

* Based on EPPO Vertebrate scheme

EFSA calculated TER values according to the Guidance document on Risk Assessment for Birds and Mammals (SANCO/4145/2000 and values above the Annex VI trigger were obtained for both acute and long-term for the use of JAU 6476 EC 250 on cereals. For the use of JAU 6476 FS 100 as seed treatment a TER of 2.77 was derived, indicating that further consideration of the long-term risk is required. A concern was raised in the experts' meeting on ecotoxicology regarding developmental effects observed in studies with the metabolite (see below). A more elaborated justification for the choice of endpoint was provided by the RMS before the evaluation meeting in April 2007 (see Addendum 13) and it was agreed by Member States to use the NOELrepro of 95.6 mg/kg bw/day for the long-term risk assessment for prothioconazole.

Prothioconazole-desthio was considered to be the only major metabolite in cereal foliage. A total conversion of prothioconazole to the desthio metabolite was assumed in the risk assessment. The long-term risk assessment in the DAR was based on a NOELrepro of 10 mg/kg bw/day from a 2-generation study. In the PRAPeR expert meeting Member State experts questioned why the increase in foetal abnormalities observed in the rabbit developmental study were disregarded. The RMS considered these slight increases to have no impact at the population level. As for prothioconazole, a more elaborated justification for the choice of endpoint was provided by the RMS before the evaluation meeting in April 2007 (see Addendum 13) and it was agreed by Member States to use the NOELrepro of 10 mg/kg bw/day for the long-term risk assessment for the metabolite.

Summary of the risk assessment for herbivorous mammals exposed to prothioconazole-desthio

Active substance: Prothioconazole-desthio	1st tier TER*	Proposed refinements	Conclusion of peer review
JAU 6476 EC 250 cereals			
Acute risk	SHM: >46	Not necessary	Low acute risk
Long-term/reproductive risk	SHM: **2.38**	Measured maximum residues in wheat of 3.7 mg/kg) and a mean DT_{50} of 3.2 days. TER calculated according to SANCO/4145/2000	Low long-term risk Refined TER = 7.2
JAU 6476 EC 250 oilseed rape			
Acute risk	Covered by cereal assessment	Not necessary	Low acute risk
Long-term risk	MHM: 7.1**	Not necessary	Low long-term risk
JAU 6476 FS 100 Cereal seed treatment			
Acute risk	SGB: >46	Not necessary	Low acute risk
Long-term risk	SGB: 6.4 (based on measured residue)	Maximum mean daily level on treated seed remaining on soil surface averaged over 0 to 9 day exposure and normalised to a use rate of 15 g a.s./100 kg seed (3 field trials)	TER = **1.7** calculated by EFSA using the $NOEL_{repro}$ of 10 mg/kg bw/day in accordance with SANCO/4145/2000 Further data/information to address the risk was considered necessary by the PRAPeR 03 expert meeting.

LHB: Large herbivorous bird; IB: Insectivorous bird; SGB: Small granivorous bird; NA: Not assessed

* Based on EPPO Vertebrate scheme

** Calculated by EFSA in accordance with SANCO/4145/2000

The long-term risk assessment for herbivorous mammals was refined in the same way as for birds by using measured residue levels of prothioconazole-desthio in green parts of cereals and a mean DT_{50} calculated from 8 trials. This resulted in TERlt above the Annex VI trigger.

No assessment of the risk to birds and mammals from intake of contaminated drinking water from puddles and/or leaf axils is available and this should also be considered at Member State level.

Secondary poisoning

The risk to earthworm- and fish-eating birds and mammals from secondary poisoning was considered to be low based on the low BCF in fish and short depuration rates for both prothioconazole and the desthio metabolite

In summary, the risk to birds and mammals from the use of prothioconazole as a foliar application in cereals and oilseed rape with the formulation JAU 6476 EC250 is considered to be low. The assessment of long-term risk for birds and mammals from the use as cereal seed treatment indicates a high risk based on the available and peer reviewed data and information.

5.2. RISK TO AQUATIC ORGANISMS

Prothioconazole is proposed to be classified as R51 based on the lowest EC_{50} of 1.1 mg a.s./L obtained for algae. Since the substance is not ready biodegradable, it will also be assigned R53. The acute toxicity of the formulation JAU 6476 EC 250 is of similar acute toxicity as technical prothioconazole.

The acute and long-term risk to aquatic organisms from spray application of JAU 6476 EC 250 was estimated by comparing the PECsw resulting from 90th percentile drift to a 30 cm deep water body at 1 m distance from the treated field. All TER values were well above the relevant Annex VI trigger indicating a low risk (the lowest TERa was 543 and the lowest TERlt was 304).

Metabolites

Two major metabolites were detected in the water/sediment study, prothioconazole-desthio and 1,2,4-triazole. The metabolite prothioconazole-S-methyl was considered to be a major metabolite in soil and thus might contaminate surface water via drainage and/or run-off. Toxicity studies show that the desthio metabolite is of less or similar acute toxicity to fish and daphnids. It is of higher toxicity towards algae and approximately 100 times more toxic to fish in early life stage toxicity studies. The NOEC was based on reduction in total length partly due to a deformation of the head which showed a dose response. The TERlt based on the PECsw derived from the spray drift from application of 3 × 200 g a.s./ha at 1 m was 2.9. With a buffer zone of 5 m the TER was calculated to 14.1. 1,2,4-triazole is of lower toxicity than prothioconazole and can be regarded as not ecotoxicologically relevant. The acute toxicity to fish and daphnids from prothioconazole-S-methyl and the toxicity to algae are in the similar to prothioconazole and this metabolite can be considered as not ecotoxicologically relevant.

In the experts' meeting a concern was raised regarding possible endocrine effects from the metabolite prothioconazole-desthio. One Member State informed that a full life cycle study had been requested during a national authorisation process. The study has now also been submitted also to the RMS but has not yet been evaluated. EFSA recommends that the study is evaluated before a final conclusion on the risk to fish is drawn.

Risk to sediment dwelling organisms

Prothioconazole and the desthio metabolite may partition and persist in sediment. NOECs from water spiked tests with *Chironomus riparius* were compared with PECsw estimated from spray drift at 1 m. The TER values for both prothioconazole and the metabolite were well above the Annex VI trigger and thus indicate that the risk to sediment dwelling organisms is low.

Bioaccumulation

The BCF in whole fish for prothioconazole was determined as 19.7 and as 65 for the metabolite prothioconazole-desthio. Both the parent and the metabolite were rapidly depurated. The log Pow for the 1,2,5-triazole was stated by the applicant to be <3 and bioconcentration would therefore be of no concern. The metabolite prothioconazole-S-methyl has a predicted log Pow of 4.19. No bioconcentration study is available since the concentration in surface water was predicted to be low from the information available at the time of dossier submission. Bioconcentration of prothioconazole-S-methyl should be considered at Member State level should MS surface water exposure assessment show that this metabolite may contaminate surface water from drainage and/or run-off.

In conclusion, risk mitigation measures comparable to 5 m spray free buffer zones are required to protect the aquatic environment based on the currently evaluated data and information. EFSA recommends that the available full life cycle study with the metabolite prothioconazole-desthio is evaluated before a final conclusion on the risk to fish is drawn.

5.3. RISK TO BEES

Bees may be exposed to prothioconazole at foliar application of JAU 6476 EC 250 when foraging on aphid honey dew or flowering weeds. No exposure is expected from the formulation JAU 6476 FS 100 on seeds. Results from acute oral and contact studies with technical prothioconazole and the formulation JAU 6476 EC 250 indicate a low toxicity. The calculated hazard quotients are in the range of 1.0 to 4.1, which is well below the Annex VI trigger of 50 indicating a low risk.

5.4. RISK TO OTHER ARTHROPOD SPECIES

The LR_{50} for the standard species, *Aphidius rhopalosiphi* and *Typhlodromus pyri*, were estimated to be 139.9 and 18.7 g a.s./ha based on glass plate studies with the formulation JAU 6476 EC 250. Hazard quotients (HQ) were calculated for in-field and off-field situations in accordance with the guidance in ESCORT 2 assuming a 3 application of 200 g a.s./ha for the in-field situation and 90th percentile drift from a single application at 1 m from the treated field for the off-field situation. The in-field HQ for *T. pyri* was 10.7, hence indicating a potential risk, while the value for *A. rhopalosiphi* was 1.4 and thus below the trigger of 2. Off-filed HQ values were well below the trigger for both species. The LR_{50} for *T .pyri* in an extended laboratory study was 445.5 g a.s./ha and effects on reproduction were below 50% (47% at 245 g a.s./ha and 40% at 380 g a.s./ha). No adverse effects on reproduction were observed in a study using 14 days aged residues of 300 g a.s./ha. Additional studies with *Coccinella septempunctata* and *Chrysoperla carnea* indicate that no adverse effects on foliage dwelling non-target arthropods will occur from the proposed application rate of 3 × 200 g a.s./ha. Studies using the ground dwelling arthropods *Poecilus cupreus* and *Aleochara bilineata* showed no effects >30% up to application rates of 400 g a.s./ha for *A. bilineata* and 600 g a.s./ha for *P. cupreus*. It was concluded that the risk to non-target arthropods from the use of JAU 6476 EC 250 is expected to be low.

Effects on ground dwelling non-target arthropods were also studied using seeds dressed with the formulation JAU 6476 FS 100. No adverse effects were observed. However, the dose rate used in the studies (19.3 to 22.5 g a.s./ha) did not cover the proposed application rate of 34 5 g a.s./ha. However, since no adverse effects were observed on *F. candida* at 112.5 g a.s./ha, and the risk to ground dwelling arthropods from higher rates of prothioconazole resulting from the spray application was considered to be low, it was agreed in the PRAPeR expert meeting that the risk from the use of JAU 6476 FS 100 as seed dressing is expected to be low.

5.5. RISK TO EARTHWORMS

Acute toxicity studies with technical prothioconazole and the formulated product JAU 6476 EC 250 showed a low toxicity towards earthworms. The acute TER values were >3759 and >937, respectively, when the LC_{50} was compared with a worst case PEC_{soil} of 0.133 mg a.s./kg soil calculated for a seed treatment followed by the first spray application, hence indicating a low risk. Neither were any adverse effects observed in chronic studies performed with the formulations JAU 6476 EC 250 and JAU 6476 FS100 at the highest concentrations tested which corresponded to 1000 g a.s./ha for the EC formulation and 122 g a.s./ha for the FS formulation. The long-term TER for the use of JAU 6476 EC 250 was 5.0 based on the worst case PEC_{soil}. The TER of 5 is just at the Annex VI trigger. However, since no effects were observed at the highest treatment level and prothioconazole degrades rapidly in soil, the long-term risk from exposure to parent prothioconazole is expected to be low. This was confirmed by a field study performed at a grassland site in Germany where no adverse effects on five different species were observed following three applications of JAU 6476 EC250, each corresponding to 200 g a.s./ha, except a 46% reduction in number of *Aporrectodea caliginosa* juveniles 7 weeks after the first application. No adverse effects were observed after 5 months.

Acute and chronic toxicity studies were also available with the metabolites prothioconazole-desthio and prothioconazole-S-methyl. Both metabolites exhibited a low acute toxicity (LC_{50} >100 mg/kg d.wt. soil). However, significant reduction in the number of offspring was observed in the chronic studies. The long-term TER values were calculated to 1352 for the S-methyl and to 3.5 for the des-thio. Since no log P_{ow} values were available, the NOECs were corrected for high organic content of the artificial soil used in the tests. A worst case PEC_{soil} from application as seed treatment followed by three spray applications were used. Some concerns regarding the validity of the chronic study with the desthio metabolite was raised during the peer review since the number of juveniles in the control was too low. However, it was concluded in the experts' meeting that since the field study did not show adverse long-term risk to earthworms the risk from both the parent and metabolites is low.

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

Studies of effects on *Folsomia candida* were available using technical prothioconazole, the soil metabolites prothioconazole-desthio and prothioconazole-S-methyl and two studies using seeds treated with the formulated product JAU 6476 FS100. Additionally, an extended laboratory study with the soil predatory mite, *Hypoaspis aculeifer* was available with technical prothioconazole and a

litter bag study using wheat seeds treated with JAU 6476 FS100 at a rate corresponding to 23 g a.s./ha followed by 3 spray applications at 200 g a.s./ha with JAU 6476 EC 250.

TER values for *F. candida* and *H. aculeifer* were 240 and 1250, respectively, based on NOECs for prothioconazole and a worst case PEC_{soil} of 0.133 mg a.s./kg soil (maximum after seed treatment + foliar application). The TER values for *F. candida* were 218 and 427, respectively, for the desthio and S-methyl metabolites. No adverse effects on litter degradation were observed in the litter bag study.

Effects on the number of juvenile *F. candida* were observed in one of the studies using treated seeds. In that study seeds were sown at 0.5 cm in an overall soil depth of 1.3 cm. In the second study seeds were sown at 2.5 cm in an overall depth of 5 cm and no effects were observed at the highest sowing rate of 1150 kg seed/ha (corresponding to 112.35 g a.s./ha). In conclusion the risk to soil macro-organisms was considered to be low.

5.7. RISK TO SOIL NON-TARGET MICRO-ORGANISMS

Effects on soil nitrogen transformation and soil respiration were studied using technical prothioconazole and the metabolite prothioconazole-S-methyle. No effects >25% were observed for a period of 28 days at concentrations corresponding to 1 and 10 times the proposed application rate of parent prothioconazole. Effects on soil nitrogen turnover were also studied with the metabolite prothioconazole-desthio. No effects >25% were observed for a period of 42 days at a concentrations corresponding to 1 times the proposed application rate of parent prothioconazole or for 28 days at a rate corresponding to 5 times the proposed application rate. Potential effects on soil respiration from the desthio-metabolite were considered to be covered by the study with parent prothioconazole since prothioconazole is rapidly degraded.

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

No exposure of non-target plants off-field is expected from the use of prothioconazole as a seed treatment. Visual assessment of of phytotoxic symptoms was made for six dicot and 5 monocot species following application of technical prothioconazole or the formulation JAU 6476 EC250. The lowest concentration of technical prothioconazole showing ≥50% effect was 1000 g/ha. One species showed effects ≥50% in the study with the formulation at a dose rate corresponding to 600 g a.s./ha. At 200 g a.s./ha (maximum proposed dose rate) low levels of phytotoxicity was reported (≤10% in 2 species). The risk to non-target plants outside the treated field from the use of JAU 6476 EC250 is therefore considered to be low. No exposure of non-target plants off-field is expected from the use of prothioconazole as a seed treatment.

5.9. RISK TO BIOLOGICAL METHODS OF SEWAGE TREATMENT

The EC_{50} was determined as >10000 mg a.s./L in an activated sludge respiration inhibition test. The maximum initial PEC in surface water from use as a foliar spray is 0.0018 mg a.s./L. No adverse

effects on biological methods of sewage treatment are therefore expected should prothioconazole reach sewage treatment plants.

6. Residue definitions

Soil

Definitions for risk assessment: prothioconazole, prothioconazole-desthio (M04)[13], prothioconazole-S-methyl (M01)[14]

Definitions for monitoring: prothioconazole, prothioconazole-desthio (M04)

Water

Ground water

Definitions for exposure assessment: prothioconazole, prothioconazole-desthio (M04), prothioconazole-S-methyl (M01)

Definitions for monitoring: prothioconazole, prothioconazole-desthio (M04)

Surface water

Water

Definitions for risk assessment: prothioconazole, prothioconazole-desthio (M04), 1,2,4-triazole

Definitions for monitoring: prothioconazole, prothioconazole-desthio (M04)

Sediment

Definitions for risk assessment: prothioconazole, prothioconazole-desthio (M04)

Definitions for monitoring: prothioconazole

Air

Definitions for risk assessment: prothioconazole, prothioconazole-desthio (M04)

Definitions for monitoring: prothioconazole, prothioconazole-desthio (M04)

Food of plant origin

Definitions for risk assessment: Sum of prothioconazole-desthio and all metabolites containing the 2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl-2H-1,2,4-triazole moiety, expressed as prothioconazole-desthio (provisional)

Definitions for monitoring: prothioconazole-desthio

[13] M04 = 2-(1-chlorocycloproyl)1-(2-chlorophenyl)-3-(1,2,4-triazol-1-yl)-propan-2-ol

[14] M01 = 2-(1-chlorocyclopropyl)-1-(2-chlorophenyl)-3-(4,5-dihydro-5-methylthio-1,2,4-triazolyl-1)-propan-2-ol

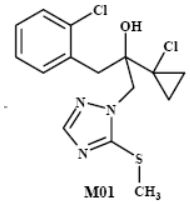
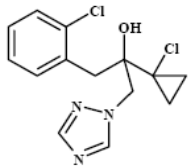
Food of animal origin

Definitions for risk assessment: Sum of prothioconazole-desthio and all metabolites containing the 2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl-2H-1,2,4-triazole moiety, expressed as prothioconazole-desthio (provisional)

Definitions for monitoring: Sum of prothioconazole-desthio and its glucuronide conjugate, expressed as prothioconazole-desthio

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

Soil

Compound (name and/or code)	Persistence	Ecotoxicology
prothioconazole	Very low to low persistent (1^{st} order labDT$_{50}$ = 0.07 – 1.27 days at 20ºC and 48-49% MWHC)	Low risk
prothioconazole-S-methyl (M01) 	Low to moderate persistent (1^{st} order labDT$_{50}$ = 5.9 – 46.0 days at 20ºC and 48-49% MWHC)	Low risk
prothioconazole-desthio (M04) 	Low to moderate persistent (1^{st} order labDT$_{50}$ = 7.0 – 34.0 days at 20ºC and 48-49% MWHC)	Low risk

Ground water

Compound (name and/or code)	Mobility in soil	> 0.1 µg / L 1m depth for the representative uses (at least one FOCUS scenario or relevant lysimeter)	Pesticidal activity	Toxicological relevance	Ecotoxicological relevance
prothioconazole	Low mobile (K_{oc} = 1765 mL/g, determined in aged column leaching study)	FOCUS-PELMO modelling: no	Yes	Yes	Yes
prothioconazole-S-methyl (M01)	Low to slight mobile (K_{foc} = 1974 - 2995 mL/g)	FOCUS-PELMO modelling: no	No assessment required	No assessment required, no data available	No
prothioconazole-desthio (M04)	Low mobile (K_{foc} = 523 - 625 mL/g)	FOCUS-PELMO modelling: no	No assessment required	Yes	Yes

Surface water and sediment

Compound (name and/or code)	Ecotoxicology
prothioconazole (water and sediment)	Toxic to aquatic organisms (R51) but a low risk was concluded.

Compound (name and/or code)	Ecotoxicology
prothioconazole-desthio (M04) (water and sediment)	100 times more toxic to fish (ELS) compared to prothioconazole. Risk mitigation required.
1,2,4-triazole (M13) (water) 	Lower toxicity than prothioconazole. Not of ecotoxicological relevance.

Air

Compound (name and/or code)	Toxicology
prothioconazole	Not acutely toxic via inhalation (LC_{50} > 4990 mg/m3)
prothioconazole-desthio (M04)	No data available on toxicity via inhalation route

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

- A revised specification is required to include a proposed maximum limit for the relevant impurity prothioconazole-desthio and to correct the naming of the impurities with regard to R and S isomers (relevant for all uses evaluated, data gap identified by EFSA February 2007. Refer to chapter 1).
- An analytical method is required for the relevant impurity toluene in both the EC and FS formulation (relevant for all uses evaluated, data gap identified by EFSA February 2007. Refer to chapter 1).
- An analytical method is required for the relevant impurity prothioconazole-desthio in both the EC and FS formulation (relevant for all uses evaluated, data gap identified by EFSA February 2007; refer to chapter 1).
- Storage stability study is required for both the EC and FS formulations where the relevant impurity prothioconazole-desthio is analysed for before and after storage (relevant for all uses evaluated, data gap identified by EFSA February 2007; refer to chapter 1).
- An analytical method is required for the relevant impurity prothioconazole-deschloro in both the EC and FS formulation (relevant for all uses evaluated, data gap identified by EFSA April 2007; refer to chapter 1).
- Storage stability study is required for both the EC and FS formulations where the relevant impurity prothioconazole-deschloro is analysed for before and after storage (relevant for all uses evaluated, data gap identified by EFSA April 2007; refer to chapter 1).
- Spectra for the relevant impurity prothioconazole-deschloro (relevant for all uses evaluated, data gap identified by EFSA April 2007; refer to chapter 1).
- Validated method of analysis to monitor the glucuronide conjugate in products of animal origin (relevant for all uses evaluated, data gap identified by EFSA April 2007; refer to chapter 1).
- A comparison of the mode of action of prothioconazole and the triazole metabolite derivatives is required in order to assess the toxicity resulting of the combined exposure to these compounds (relevant for all uses evaluated, data gap identified by EFSA after the expert meetings on mammalian toxicology and residues in January 2007; refer to chapter 2.8).
- Information allowing the assessment consumer exposure to triazole metabolite derivatives in primary crops, rotational crops, and products of animal origin (relevant for all uses evaluated, data gap identified by EFSA resulting from expert meetings on mammalian toxicology and residues in January 2007; refer to chapter 3)

<u>JAU 6476 FS100 (cereal seed treatment)</u>

- The long-term risk to granivorous birds need to be further addressed (relevant for the use as cereal seed treatment; refined assessment submitted to the RMS but not evaluated or peer reviewed; refer to point 5.1)

- The long-term risk to granivorous mammals need to be further addressed (relevant for the use as cereal seed treatment; refined assessment submitted to the RMS but not evaluated or peer reviewed; refer to point 5.1)

JAU 6476 EC250 (cereals)

- A full life cycle study with the metabolite prothioconazole-desthio should be evaluated before a final conclusion on the risk to fish is drawn (relevant for the use as foliar application; study submitted to the RMS but not evaluated or peer reviewed; refer to point 5.1)

CONCLUSIONS AND RECOMMENDATIONS

Overall conclusions

The conclusion was reached on the basis of the evaluation of the representative uses as a fungicide as proposed by the applicant which comprises foliar application to wheat, rye, triticale, barley, oats and oilseed rape and as a seed treatment to the same crops excluding oilseed rape. Full details of the application rates and timings can be found in the attached end points.

There are two representative formulated products evaluated Proline an emulsifiable concentrate (EC) formulation and Redigo a flowable concentrate for seed treatment (FS) formulation.

Methods are available to monitor all compounds given in the respective residue definition for food of plant origin, water, soil and air. Residues in food of plant origin can be determined with a multi-method (The German S19 method has been validated for prothioconazole-desthio). Only single methods are available to determine residues of prothioconazole-desthio, in products of animal origin and prothioconazole, prothioconazole-desthio in soil water and air. A method is not available to monitor the glucuronide conjugate in products of animal origin. Also if the active is classified as toxic then methods for body fluids and tissues would need to be considered.

Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that at least some quality control measurements of the plant protection product are possible. Methods for the relevant impurities in the formulation are not available.

Prothioconazole is of low acute oral, dermal and inhalation toxicity; it does not show any eye and skin irritation or sensitising potential. The relevant short term oral NOAEL is 25 mg/kg bw/day and the chronic NOAEL is 5 mg/kg bw/day. Prothioconazole does not show *in vivo* genotoxic and carcinogenic potential. The relevant reproductive NOAEL is 95.6 mg/kg bw/day, while the developmental NOAEL is 20 mg/kg bw/day. Prothioconazole was proposed to be classified as Repro cat 3, R 63 (Repro cat 2?), based on the increased incidences of microphthalmia in one out of two rat strains tested. The major metabolite prothioconazole-desthio (M04) has been shown to be more toxic in developmental studies with rats and rabbits. The proposed ADI for prothioconazole is 0.05 mg/kg bw/day, and the ARfD and AOEL are 0.2 mg/kg bw. The estimated operator exposure for the 250 EC formulation is below the AOEL when PPE is worn for mechanical spraying in cereals, using the UK-

POEM and the German model. The exposure to operators working at the treatment of seeds with the prothioconazole FS formulation accounts for about 55% of the AOEL for operators performing mixing/loading/calibration/cleaning and bagging. For sowing, the estimated exposure is about 4% of the AOEL. The exposure to workers after spraying in cereals is about 45% of the AOEL. Estimated exposure for bystanders is negligible

The metabolism of prothioconazole has been fully investigated in cereals, oilseeds, rotational crops as well as in livestock and mainly proceeds through oxidative reactions. In most plant parts and animal tissues, the major compound of the metabolic pattern is prothioconazole-desthio, which is more toxic than the parent compound. Given the complex plant and animal metabolic pattern and to reflect adequately the toxicological burden the consumer is exposed to, the residue definition for risk assessment in all commodities is the sum of prothioconazole-desthio and all metabolites containing the 2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl-2H-1,2,4-triazole moiety, expressed as prothioconazole-desthio.
This residue definition for risk assessment is however provisional as beside the metabolites which are structurally related to the parent compound, cereal grains, oilseeds, rotational crops and animal products are expected to contain significant amounts of non specific triazole derivative metabolites. These compounds (mainly triazole, triazole alanine and triazole acetic acid) which are common metabolites of all triazole fungicides have been recognized as hazards given their impact on reproduction. Toxicological reference values have been agreed by the PRAPeR expert meeting 14 on toxicology in January 2007.
The monitoring of plant and animal commodities can be targeted on prothioconazole-desthio, but in animal tissue, its glucuronide conjugate needs to be included in the analysis. A sufficient amount of data has been submitted in order to set MRLs.
Chronic and acute consumer exposures are well below the respective toxicological trigger values allocated to prothioconazole-desthio.
This assessment was conducted on the basis of the provisional residue definition for risk assessment and does not cover the triazole derivative metabolites. A robust conclusion on the risk for the consumer cannot be finalised at this stage. Information on the actual level of those derivatives in primary crops, rotational crops, and products of animal origin is lacking. It must be noted that this lack of data is a generic issue and concerns all active substances of the triazole chemical class whose degradation pathway in primary crops, soil and livestock involves a cleavage of the triazole ring.

The information available on the fate and behaviour of prothioconazole in the environment is generally sufficient to carry out an appropriate exposure assessment at the EU level with the following exception. Drainage and runoff routes of exposure to surface water have not been covered for prothioconazole and its metabolites prothioconazole-desthio (M04) and 1,2,4-triazole in the available EU level assessment. This exposure assessment and the associated risk assessment to aquatic organisms should be completed in national assessments made by the Member States. For the notified intended uses, the potential for groundwater exposure by prothioconazole or its potential soil

metabolites prothioconazole-S-methyl (M01) and prothioconazole-desthio (M04) above the parametric drinking water limit of 0.1 µg/L, is considered low.

The risk to birds and mammals from the use of prothioconazole as a foliar application in cereals and oilseed rape is considered to be low. The assessment of long-term risk for birds and mammals from the use as cereal seed treatment indicates a high risk based on the available and peer reviewed data and information. Risk mitigation measures to reduce spray drift input comparable to 5 m spray free buffer zones are required to protect the aquatic environment based on the currently evaluated data and information. EFSA recommends that the available full life cycle study with the metabolite prothioconazole-desthio is evaluated before a final conclusion on the risk to fish is drawn. Furthermore, bioconcentration of prothioconazole-S-methyl should be considered at Member State level should MS surface water exposure assessment show that this metabolite may contaminate surface water from drainage and/or run-off. The risk to bees, other non-target arthropods, earthworms, other non-target soil macro-organisms, soil micro-organisms, non-target plants and biological methods of sewage treatment is considered to be low.

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

- Use of personal protective equipment is needed during mechanical spraying in cereals in order to have an operator exposure below the AOEL (refer to point 2.12).
- Risk mitigation measures comparable to 5 m spray free buffer zones are required to protect the aquatic environment based on the currently evaluated data and information (refer to point 5.2).

Critical areas of concern

- The metabolite prothioconazole-desthio is more toxic than prothioconazole in the rat and rabbit developmental studies (the classification Repro cat 2, R61 is proposed)
- A method is not available to monitor the glucuronide conjugate in products of animal origin.
- A high first tier long-term risk to birds and mammals from the use as cereal seed treatment was identified based on the available and peer reviewed data and information.
- Risk mitigation measures comparable to 5 m spray free buffer zones are required to protect the aquatic environment based on the currently evaluated data and information. EFSA recommends that the available full life cycle study with the metabolite prothioconazole-desthio is evaluated before a final conclusion on the risk to fish is drawn.
- A final consumer risk assessment covering the toxicological burden of the triazole derivative metabolites is at this stage not possible to conduct due to lacking data on their occurrence in primary crops, rotational crops and products of animal origin.

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

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

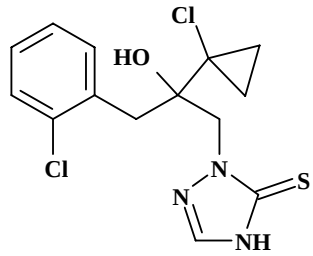
Appendix 1.1: Identity, Physical and Chemical Properties, Details of Uses, Further Information

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

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	(*RS*)-2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-2,4-dihydro-1,2,4-triazole-3-thione
Chemical name (CA) ‡	2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1,2-dihydro-3H-1,2,4-triazole-3-thione
CIPAC No ‡	745
CAS No ‡	178928-70-6
EEC No (EINECS or ELINCS) ‡	Not allocated
FAO Specification ‡ (including year of publication)	Not available
Minimum purity of the active substance as manufactured ‡ (g/kg)	≥ 970 g/kg
Identity of relevant impurities (of toxicological, environmental and/or other significance) in the active substance as manufactured (g/kg)	Toluene 5 g/kg 2-(1-chlorocyclopropyl)-1-(2-chlorophenyl)-3-(1H-1,2,4-triazol-1-yl)-2-propanol (prothioconazole-desthio) level not defined 2-[2-(1-chlorocyclopropyl)-2-hydroxy-3-phenylpropyl]-2,4-dihydro-3H-1,2,4-triazole-3-thione (prothioconazole –deschloro) level not yet accepted.
Molecular formula ‡	C_{14} H_{15} Cl_2 N_3 O S
Molecular mass ‡	344.26 g/mol

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

Structural formula ‡ Prothioconazole (JAU 6476)	

Physical-chemical properties (Annex IIA, point 2)

Melting point (state purity) ‡	139.1 °C - 144.5 °C
Boiling point (state purity) ‡	487 °C ± 50 °C
Temperature of decomposition	Thermally stable at ambient temperature under air
Appearance (state purity) ‡	Technical and pure was white to faintly beige powder (99.4%/97%)
Relative density (state purity) ‡	Density = 1.36 g/mL at 20°C (99.4%)
Surface tension	67 mN/m at 20 °C, Test concentration 7.6 mg/L
Vapour pressure (in Pa, state temperature) ‡	<< 4 x 10^{-7} Pa at 20 °C << 4 x 10^{-7} Pa at 25 °C
Henry's law constant (Pa m^3 mol^{-1}) ‡	<< 3 x 10^{-5} Pa x m^3 / mole at 20 °C
Solubility in water ‡ (g/L or mg/L, state temperature)	pH 4: 0.005 g/L at 20 °C pH 8: 0.3 g/L at 20 °C pH 9: 2.0 g/L at 20 °C
Solubility in organic solvents ‡ (in g/L or mg/L, state temperature)	n-heptane <0.1 g/L at 20 °C xylene 8 g/L at 20 °C 1-octanol 58 g/L at 20 °C 2-propanol 87 g/L at 20 °C ethyl acetate >250 g/L at 20 °C polyethylene glycol (PEG) >250 g/L at 20 °C acetonitrile 69 g/L at 20 °C acetone >250 g/L at 20 °C dimethylsulfoxide 126 g/L at 20 °C dichloromethane 88 g/L at 20 °C
Partition co-efficient (log POW) ‡ (state pH and temperature)	Prothioconazole pH — log Pow — Temperature unbuffered — 4.05 — 20 °C pH 4 — 4.16 — 20 °C pH 7 — 3.82 — 20 °C pH 9 — 2.00 — 20 °C

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

Partition co-efficient (log POW) ‡ (state pH and temperature)	pH Desthio-prothioconazole (M04, SXX 0665) pH: Unbuffered, bidistilled water; log Pow: 3.04; Temperature: 22 °C
Hydrolytic stability (DT_{50}) ‡ (state pH and temperature)	Temperature / pH / DT_{50} 50°C / pH 9 and 7 / > 1 year 50°C / pH 4 / 120 days 25°C / pH 9, 7 and 4 / > 1 year
Dissociation constant ‡	pKa = 6.9
UV/VIS absorption (max.) ‡ (if absorption > 290 nm state ε at wavelength)	Maximum absorbance at 267 nm (ε= 13937 l mol^{-1} cm^{-1}).
Photostability (DT_{50}) ‡ (aqueous, sunlight, state pH)	DT_{50} at pH 7 (sterile aqueous phosphate buffer), exposed to simulated sunlight (Suntest®) at 25°C: experimental half-life: 47.7 hours (n = 2), corresponding to a predicted environmental half-life under solar summer conditions (June) of Phoenix, AZ, USA of 7.1 days and 11 days at Athens
Quantum yield of direct phototransformation in water at Σ > 290 nm ‡	The mean quantum yield was calculated to be Φ = 0.0638 (pH 4) and 0.0047 (pH 9).
Flammability ‡	Not highly flammable
Explosive properties ‡	Not explosive

‡ Endpoints identified by the 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	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of a.s. (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hl min max	water l/ha min max	kg as/ha min max		
wheat, rye, triticale	EU North South	Proline	F	Rusts, Eyespot, Fusarium spp., Powd. Mildew, Rhynchospor., Septoria,	EC	250 g/L	overall spray	start 26-29 up to BBCH69 (interval 14 - 21 d)#	1 – 3 #	ref. to growth stage		200 - 400	0.2	35	# timing , no. of applic. depends on national conditions
barley, oat	EU North South	Proline	F	Rusts, Eyespot, Pyren. teres, Powd. Mildew, Fusarium spp., Rhynchospor.	EC	250 g/L	overall spray	start 30 up to BBCH 61 (interval 14 - 21 d)#	1 – 2 #	ref. to growth stage		200 - 400	0.2	35	# timing , no. of applic. depends on national conditions
rape	EU North	Proline	F	Sclerotinia, Botrytis, Alternaria, Leptosphaeria	EC	250 g/L	overall spray	start BBCH 53 (interval 14 - 28 d)#	1 – 2 #	ref. to growth stage		200 - 400	0.175	56	# timing , no. of applic. depends on national conditions
wheat, rye, triticale, oat, barley	EU North South	Redigo	F	Fusarium spp., Bunt, Smut	FS	100 g/L	seed treat-ment	pre sowing	1	n.a. (0)		200 – 400 ml water /dt	*approx. 9-18 g as/ha (180 kg seed/ha)	n.a.	*5 – 10 g as/dt seed [1]

[1] A high first tier high risk to birds and mammals was identified

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

Remarks: * Uses for which risk assessment could not been concluded due to lack of essential data are marked grey

(a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)

(b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)

(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds

(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)

(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989

(f) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench

(g) All abbreviations used must be explained

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

(i) g/kg or g/L

(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application

(k) The minimum and maximum number of application possible under practical conditions of use must be provided

(l) PHI - minimum pre-harvest interval

(m) Remarks may include: Extent of use/economic importance/restrictions

‡ Endpoints identified by the 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)	HPLC and UV detection with internal standard
Impurities in technical as (principle of method)	HPLC and UV detection with external standard
Plant protection product (principle of method)	HPLC and UV detection with external standard

Analytical methods for residues (Annex IIA, point 4.2)

Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)	Weeren, Pelz 2000 (GC-MS, JAU6476-desthio) LOQ Wheat, Barley (Forage, Straw): 0.05 mg/kg LOQ Wheat, Barley (Grain), Canola (Seed), Tomato, Orange (Fruit): 0.02 mg/kg
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)	Heinemann 2001b (HPLC-MS/MS, JAU6476-desthio, JAU6476-3-hydroxy-desthio, JAU6476-4-hydroxy-desthio) LOQ Milk: 0.004 mg/kg LOQ Meat, Liver, Kidney, Fat: 0.01 mg/kg Open: there is no method available for the glucuronide conjugate
Soil (principle of method and LOQ)	Schramel 2000 (HPLC-MS/MS, JAU6476, JAU6476-desthio, JAU6476-S-methyl*) * for monitoring not needed LOQ Soil: 0.006 mg/kg Add'l method: Steinhauer 2001 (GC-MS, JAU6476-desthio) LOQ Soil: 0.01 mg/kg
Water (principle of method and LOQ)	Sommer 2001b (HPLC-MS/MS, JAU6476, JAU6476-desthio) LOQ Surface and Drinking water: 0.1 µg/L for JAU6476 and 0.05 µg/L for JAU6476-desthio
Air (principle of method and LOQ)	Maasfeld 2002a (HPLC-MS/MS, JAU6476) LOQ Air: 0.015 mg/m^3 Additional method: Maasfeld 2002b (HPLC-MS/MS, JAU6476-desthio) LOQ Air: 0.0006 mg/m^3

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

Body fluids and tissues (principle of method and LOQ)	Open, data will be required if ECB classify the active as toxic

Classification and proposed labelling (Annex IIA, point 10)

with regard to physical/chemical data	None

‡ Endpoints identified by the 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 ‡	JAU 6476: Rapid and nearly complete (peak plasma levels less than 1 h after dosing > 90 % of dose absorbed within 48 h after dosing JAU 6476-desthio (M04): Rapid and nearly complete (peak plasma levels at 1-1.5 h after dosing > 90 % of dose absorbed within 48 h after dosing
Distribution ‡	JAU 6476: Broad distribution, but primarily to liver and kidney JAU 6476-desthio (M04): Limited distribution to peripheral tissues; mainly to liver and renal cortex, intensive enterohepatic re-circulation
Potential for accumulation ‡	None
Rate and extent of excretion ‡	JAU 6476: The excretion of radioactivity is almost complete within 48 hours of oral administration Approximately 90 - 100 % of orally administered doses was excreted with urine, faeces, or bile within 7 days of treatment, JAU 6476-desthio (M04): Between 68 and 74 % was excreted with the faeces and about 10 % in urine.
Metabolism in animals ‡	JAU 6476: JAU 6476 is extensively metabolised to 18 metabolites, with the major metabolic reactions being desulfuration, oxidative hydroxylation of the phenyl moiety, and conjugation with glucuronic acid. Two major metabolites formed, JAU 6476-desthio (M04) and JAU 6476-S- or O-glucuronides (M06 or M07), and parent JAU 6476, each account for ≥10 % of the administered dose. 1,2,4-triazole (M13), occurs in urine at up to 2.3 % of the administered dose. JAU 6476-desthio (M04): Metabolism proceeds via oxidation reactions on the phenyl moiety only with subsequent glucuronidation and methylation of the oxidation products. The cyclopropyl and triazole ring structures of JAU 6476-desthio remain intact.

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

Toxicologically significant compounds ‡ (animals, plants and environment)	All main metabolites identified in plants were also detected in the rat metabolism study. For the following minor crop metabolites, further tests were conducted (acute oral toxicity test, Ames-test, and in some cases 90 d repeat dose/terato studies): JAU 6476-triazolinone (M03), JAU 6476-α-hydroxy-desthio (M18), JAU 6476-α-acetoxy-desthio (M19) JAU 6476-sulfonic acid (M02) and JAU 6476-benzylpropyldiol (M09). The tests did not show they possessed more serious toxicological potential than the parent compound.

Acute toxicity (Annex IIA, point 5.2)

	JAU 6476:	JAU 6476-desthio (M04):
Rat LD_{50} oral ‡	> 6200mg/kg	>2500 mg/kg
Rat LD_{50} dermal ‡	> 2000mg/kg	>5000 mg/kg
Rat LC_{50} inhalation ‡	> 4990mg/m³	>5077 mg/m^3 (dust)
Skin irritation ‡	Non-irritant	Non-irritant
Eye irritation ‡	Non-irritant	Slightly irritating
Skin sensitization ‡ (test method used and result)	Non-sensitizer (pilot) Skin sensitizer∗ (large scale) **R43**	Non-sensitizer

Short term toxicity (Annex IIA, point 5.3)

	JAU 6476:	JAU 6476-desthio (M04):
Target / critical effect ‡	Liver, kidney	Liver
Lowest relevant oral NOAEL / NOEL ‡	25 mg/kg bw /day (dog)	1.6 mg/kg bw/day (dog)
Lowest relevant dermal NOAEL / NOEL ‡	>1000 mg/kg bw /day (rat)	No dermal study submitted – as this material is a metabolite.
Lowest relevant inhalation NOAEL / NOEL ‡	not relevant	

∗ Evaluation meeting (24-26/04/2007): the impurity JAU 6476-deschloro, shown to be a skin sensitizer, is increased above the trigger value for classification in the technical specification of the large scale production. In the absence of a new skin sensitization test for the new technical specification, the classification R43 is proposed.

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

Genotoxicity ‡ (Annex IIA, point 5.4)	JAU 6476: Induces chromosome aberrations in Chinese hamster lung cells *in vitro*. Inconsistent/equivocal results for induction of mutations in mammalian cells *in vitro* (considered to be positive on a precautionary basis). Negative results in *in vivo* assays (rat liver UDS and two mouse bone marrow micronucleus assays). Overall, no genotoxic potential JAU 6476-desthio (M04): No genotoxic properties

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

	JAU 6476:	JAU 6476-desthio (M04):
Target/critical effect ‡	Liver, kidney	Liver
Lowest relevant NOAEL / NOEL ‡	5 mg/kg bw /day (rat, dog)	1.1 mg/kg bw /day (rat)
Carcinogenicity ‡	not carcinogenic	not carcinogenic

Reproductive toxicity (Annex IIA, point 5.6)

JAU 6476

Reproduction target / critical effect ‡	Parental: reduced - weight gain, thymus weight; increased - food intake, liver weight; reproductive: reduced - implantations and litter size. Also disruption of the oestrus cycle, mixed with general toxic effects.
Lowest relevant reproductive NOAEL / NOEL ‡	Parental: 9.7 mg/kg bw /day offspring: 95.6 mg/kg bw /day (NOAEL) reproductive: 95.6 mg/kg bw /day (NOAEL)
Developmental target / critical effect ‡	Parental: mortality, body weight loss/ decreased gain, decreased food consumption. pups: retarded ossification , reduced fetal weights, total litter losses, abortions, microphtalmia (rat) **Repro cat 3, R63**
Lowest relevant developmental NOAEL / NOEL ‡	Maternal: 80 mg/kg bw /day (rat & rabbit). developmental: 20 mg/kg bw /day (rat).*

* At PRAPeR 04 Meeting (25 – 29 September 2006), the experts considered the results of two studies (Stahl, 1997 and Young, 2004) in combination to determine the developmental NOAEL.

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

JAU 6476-desthio (M04)

Reproduction target / critical effect	Dystocia (rat 2-generation)
Lowest relevant reproductive NOAEL / NOEL	parental: 2.5 mg/kg bw/d reproductive: 11 mg/kg bw/d offspring: 11 mg/kg bw/d
Developmental target / critical effect	Extranumerary ribs (rat) **Repro cat 2, R61**
Lowest relevant developmental NOAEL / NOEL	Rat: maternal: 30 mg/kg bw/d developmental: 1 mg/kg bw/d Rabbit: maternal: 2 mg/kg bw/d developmental: 2 mg/kg bw/d

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

……	Not relevant

Other toxicological studies ‡ (Annex IIA, point 5.8)

Data for metabolites	**M02** was shown to have a higher acute toxicity than prothioconazole (LD_{50} 300-500 mg/kg bw); it is not mutagenic in the Ames test and does not produce any skeletal, visceral or external abnormalities at high doses (750 mg/kg bw/day), in repeated dose studies it does not show adverse effects on liver and hepatic enzymes at doses up to 163 mg/kg bw/day (90 day rat study). **M03**, **M09**, **M18** and **M19** were tested for acute oral toxicity and mutagenicity *in vitro* (Ames test) showing lower acute toxicity than the parent (LD_{50} >2000 mg/kg bw) and no mutagenic potential (negative in Salmonella/microsome test).
Acute and subchronic neurotoxicity	No primary neurotoxic effects for JAU 6476 or JAU 6476-desthio (M04).

Medical data ‡ (Annex IIA, point 5.9)

……	No indication of special concern (further information required)

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

Summary (Annex IIA, point 5.10)		Value (mg/kg bw/day)	Study	Safety factor
ADI ‡	JAU 6476	0.05	rat – oncogenicity	100
	JAU 6476-desthio	0.01	rat – oncogenicity	100
AOEL ‡	JAU 6476	0.2	original & suppl. rat developm. studies combined	100
	JAU 6476-desthio	0.01	Supplementary rat developmental	100
ARfD ‡	JAU 6476	0.2	original & suppl. rat developm. studies combined	100
	JAU 6476-desthio	0.01	Supplementary rat developmental	100

Triazole metabolites*		Value (mg/kg bw/day)	Study	Safety factor
ADI	1,2,4-triazole and triazole acetic acid	0.02	rat multigeneration	1000
	triazole alanin	0.1	rat developmental	1000
ARfD	1,2,4-triazole and triazole acetic acid	0.06	rat developmental	500
	triazole alanin	0.1	rat developmental	1000

Dermal absorption (Annex IIIA, point 7.3)

Prothioconazole	No studies conducted 100% assumed for concentrate and dilutions.
JAU 6476-desthio (Desthio-prothioconazole)	*In vivo* study with rhesus monkeys. Test material was SC formulation containing 480 g/L of JAU 6476-desthio. 20% dermal absorption is appropriate for use in operator exposure calculations.

* Reference values agreed during the PRAPeR expert meeting on mammalian toxicology in January 2007.

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

Acceptable exposure scenarios (including method of calculation)

As prothioconazole can degrade to desthio-prothioconazole, exposure estimates were made for both compounds.

JAU 6476 EC 250:

Operator	German model Systemic exposure was 16% of the AOEL for prothioconazole when protective gloves are worn. UK POEM Systemic exposure was 71% of the AOEL for prothioconazole when protective gloves are worn
Workers	Assuming a 50% decline in residues and a <100% conversion to desthioprothioconazole, systemic exposures are expected to be <50% of the respective AOELs for prothioconazole and desthioprothioconazole.
Bystanders	Worst case assumption is that there is 100% conversion to desthio-prothioconazole. On the basis of generic simulated monitoring data and the worst case assumption, exposure was estimated to be 2% of the AOEL.

JAU 6476 FS 100:

Operator	**Seed treatment process** Operator exposure study Systemic exposure was estimated to be 5% and 23% of the respective AOELs for prothioconazole and desthio-prothioconazole. SeedTropex data and assuming 100% dermal penetration Systemic exposures were estimated to be 55% and 51% of the respective AOELs for prothioconazole and desthio-prothioconazole. **Loading and sowing of treated seed** Assuming 100% dermal penetration, systemic exposures were estimated to be 4% and 10 % of the respective AOELs for prothioconazole and desthio-prothioconazole.
Workers	Assuming 50% decline in residues and <100% conversion to desthio-prothioconazole, systemic exposure is estimated to be <50% of the AOEL for desthio-prothioconazole.

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

Bystanders	Bystanders should not be present. However, even if they were present, exposure would be expected to be less that that for operators.

Classification and proposed labelling (Annex IIA, point 10)

with regard to toxicological data	Parent
	Xn, Harmful;
	R43 May cause sensitisation by skin contact
	Repro cat 3, R 63* Possible risk of harm to the unborn child
	JAU 6476-desthio (M04)
	T, Toxic;
	Repro cat 2, R 61 May cause harm to the unborn child

* Based on the increased incidences of microphthalmia (at 1000 mg/kg bw/day, maternal toxic dose) in one out of two rat strains tested (Stahl, 1997). Proposal made at PRAPeR 04 Meeting (25 – 29 September 2006).

‡ Endpoints identified by the 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	Cereals (wheat), foliar and seed applications Oilseeds (peanut), foliar applications
Rotational crops	Wheat / Swiss chard / Turnips
Plant residue definition for monitoring	Prothioconazole-desthio. (JAU 6476-desthio)
Plant residue definition for risk assessment	Sum of prothioconazole-desthio and all metabolites containing the 2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl-2H-1,2,4-triazole moiety) expressed as prothioconazole-desthio. This definition is provisional and will need to be reconsidered regarding the triazole derivative metabolites
Conversion factor (monitoring to risk assessment)	2 (cereal grain and oilseeds)

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

Animals covered	Lactating ruminants (goat) laying hens (chicken)
Animal residue definition for monitoring	Sum of prothioconazole-desthio and its glucuronide conjugate, expressed as prothioconazole-desthio (JAU 4676-desthio)
Animal residue definition for risk assessment	Sum of prothioconazole-desthio and all metabolites containing the 2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl-2H-1,2,4-triazole moiety) expressed as prothioconazole-desthio. This definition is provisional and will need to be reconsidered regarding the triazole derivative metabolites
Conversion factor (monitoring to risk assessment)	10 Milk 2 Liver 10 Muscle 2 Kidney 4 Fat
Metabolism in rat and ruminant similar (yes/no)	Yes
Fat soluble residue: (yes/no)	Yes, Log P_{ow} for JAU 6476-desthio = 3.04

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

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

……	Wheat / Swiss chard / Turnips (cf. "Metabolism in plants")

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

……	JAU 6476-desthio (M04): > 1.5 years in wheat green matter > 1.5 years in wheat grain > 1.5 years in wheat straw

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

	Ruminant:	Poultry:	Pig:
	Conditions of requirement of feeding studies		
Expected intakes by livestock ≥ 0.1 mg/kg diet (dry weight basis) (yes/no - If yes, specify the level)	Yes - Dairy cattle 0.41 mg/kg DM; - beef cattle 1.02 mg/kg DM, corresponding to 0.015 and 0.044 mg/kg bw resp.	No	No
Potential for accumulation (yes/no):	No	No	No
Metabolism studies indicate potential level of residues ≥ 0.01 mg/kg in edible tissues (yes/no)	Not conclusive due to high dose level	No	No
	Feeding studies (lactating cow, 0.13 mg/kg bw) Residue levels in matrices : Mean (max) mg/kg		
Muscle	<0.01	Not required	Not required
Liver	0.02	Not required	Not required
Kidney	<0.01	Not required	Not required
Fat	<0.01	Not required	Not required
Milk	<0.004		
Eggs		Not required	

‡ Endpoints identified by the 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 GAP (mg/kg) (a)	Recommendation/ comments	MRL (mg/kg)	STMR grain (mg/kg) (b)	STMR straw (mg/kg) (b)
Wheat (foliar)	Northern EU	Grains : 11 x < 0.01 Straw: 0.08, 0.09, 0.11, 0.14, 0.15, 0.19, 020, 0.27, 0.31, 0.66, 0.72		0.01*	< 0.01	0.19
	Southern EU	Grains : 8 x < 0.01 Straw: 0.22, 0.41, 0.42, 0.52, 0.53, 0.72, 0.77, 0.85		0.01*	< 0.01	0.53
Barley (foliar)	Northern EU	Grains: 9 x < 0.01 Straw: 0.05, 0.08, 2 x 0.10, 2x 0.13, 2 x 0.14, 0.30		0.01*	< 0.01	0.13
	Southern EU	Grains: 3 x 0.02, 3 x 0.01, 2 x < 0.01 Straw: 0.16, 0.19, 0.32, 0.41, 0.42, 0.75, 2 X 1.1		0.05	0.01	0.42
Wheat (seed treatment)	Northern and Southern EU	Grains : 8 x < 0.01 Straw : 8 x < 0.05		0.01*	0.01	0.05
Rape	Northern EU	Seeds: 2 x 0.02, 1 x 0.01, 5 x < 0.01		0.05	< 0.01	
	Southern EU	Seeds: 2 x 0.01, 2 x < 0.01				

(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 the 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 (prothioconazole-desthio)	0.01 mg/kg bw/day
TMDI (% ADI) WHO European Diet	6%
NEDI (% ADI) UK Model	2 % (Infant) 3 % (Toddler) 3 % (child) 1 % (Adult)
ARfD	0.01 mg/kg bw/day
Acute exposure (% ARfD)	All NESTIs < 5% for adult population

Note: this consumer risk assessment is provisional and will need to be reconsidered regarding the triazole derivative metabolites

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

Not applicable, no residues

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

Proposed MRLs

Prothioconazole-desthio:	
Wheat	0.01* mg/kg
Triticale	0.01* mg/kg
Rye	0.01* mg/kg
Barley	0.05 mg/kg
Oats	0.05 mg/kg
Oilseed rape	0.05 mg/kg
Sum of prothioconazole-desthio and its glucuronide conjugate, expressed as prothioconazole-desthio:	
Ruminant meat	0.01* mg/kg
Liver	0.01 mg/kg
Kidney	0.01* mg/kg
Ruminant fat	0.01* mg/kg
Milk	0.004* mg/kg

*) LOQ

‡ Endpoints identified by the 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 ‡	Values are given for day 120: range: 3.0 to 10.7% AR median: 4.8% AR (n=4) (phenyl-label) range: 0.3 to 2.0% AR; median: 1.2% AR (n=2) (triazole-label)
Non-extractable residues after 100 days ‡	Values are given for day 120: range: 35.6 to 46.2% AR; median: 41.0% AR (n = 4) (phenyl-label) range: 42.6 to 48.3% AR; median: 45.5% AR (n = 2) (triazole-label)
Relevant metabolites - name and/or code, % of applied ‡ (range and maximum) at 20°C after 100 days	Prothioconazole-S-methyl *(M01)*: range at day 120: 1.5 to 10.8% AR (n = 6) (both labels) max.: 13.7% AR (phenyl-label, day 7) 14.6% AR (triazole-label, day 7) Prothioconazole-desthio *(M04)*: range at day 120: 15.1 to 42.3% (n = 6) (both labels) max.: 46.5% AR (phenyl-label, day 7) 49.4% AR (triazole-label, day 7)

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

Anaerobic degradation ‡	Not applicable (A case was presented that due to the proposed use patterns as a foliar fungicide prothioconazole will not, in general, be exposed to anaerobic conditions. However, due to the fact that a seed treatment formulation is also being considered, an anaerobic aquatic metabolism study was submitted. The anaerobic study indicated relatively rapid breakdown of parent to prothioconazole-S-methyl (M01), which seems to accumulate. This might indicate that if prothioconazole was applied to an anaerobic soil there would be significant formation of M01. However, the only major period of anaerobic conditions is likely to be in the winter, i.e. following autumn seed treatment. Drilling will only take place in relatively good aerobic conditions under which there will be relatively rapid degradation of the parent compound. Therefore, it is unlikely that there would be significant formation of M01 under field conditions.)

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

Soil photolysis ‡	Phenyl-label Mineralisation at day 15: 0.7% AR Non-extractable residues at day 15: 25.5% AR Major metabolite: prothioconazole-desthio *(M04)*: max. of 38.5% AR at day 7 (38.0% AR at day 15)

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

Method of calculation	®ModelMaker, Version 1.1, 1st order kinetics
Laboratory studies ‡ (range or median, with n value, with r^2 value)	DT_{50}lab (20°C, aerobic, soil): prothioconazole (1st order and FOMC): range: 0.07 to 1.27 days, median: 0.5 days, r^2: range: 0.981 to 1.000 (n = 4) prothioconazole-S-methyl *(M01)* (1st order) range: 5.9 to 46.0 days; median: 17.7 days, r2: range: 0.955 to 0.970 (n=4). Mean value of 15.7 days used for PELMOgw modelling. prothioconazole-desthio *(M04)* (1st order) range: 7.0 to 34.0 days; median: 24.1 days r2: range: 0.820 to 0.987 (n=4) minor metabolite 1,2,4-triazole *(M13)* (1st order)[17] range: 5.0 to 9.9 days (at 20°C and pF2/10kPa); geometric mean: 7.4 days r2: range: 0.75 to 0.95 (n=3)
	DT_{90}lab (20°C, aerobic, soil): prothioconazole (1st order and FOMC): range: 0.99 to 78.2 days, median: 4.76 days, r^2: range: 0.981 to 1.000 (n = 4)" prothioconazole-S-methyl *(M01)* (1st order) range: 19.6 to 153.0; median: 58.7 days, r2: range: 0.955 to 0.970 (n=4) prothioconazole-desthio *(M04)* (1st order) range: 23.2 to 113.0; median: 80.1 days r2: range: 0.820 to 0.987 (n=4)DT_{50}lab (10°C, aerobic):

[17] Values agreed following the discussion on triazole derivate metabolites during the experts' meeting PRAPeR 12 on fate and behaviour (January 2007).

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

	DT_{50}lab (20°C, anaerobic): (soil, aerobic, 10°C, calculated from 20°C using Arrhenius equation): prothioconazole (1st order): range: 0.20 to 2.8 days; median: 1.1 days prothioconazole-S-methyl *(M01)* (1st order) range: 12.9 to 100.9; median: 38.8 days prothioconazole-desthio *(M04)* (1st order) range: 15.3 to 74.5; median: 52.9 days
	DT_{50}/DT_{90} (soil anaerobic): Not applicable (See case under 'Route of degradation in soil - Supplemental studies')
	Degradation in the saturated zone ‡: No information submitted, none required
Field studies ‡ (state location, range or median with n value)	Location: southern (two sites) and northern (four sites) Europe, 1st order calculation prothioconazole DT_{50}f: range: 1.3 to 2.8 days, median: 1.6 days, (n = 8), r^2: range: 0.999 – 1.00. Maximum 2.8 day value used for PECsoil calculations. prothioconazole-desthio *(M04)* DT_{50}f: range: 16.3 to 72.3 days, median: 42.2 days (n = 8), r2: range: 0.91 – 0.98. (Maximum 72.3 days value and 57.1% conversion rate used for PECsoil calculations).

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

Field studies ‡ (state location, range or median with n value)	prothioconazole: $DT_{90}f$: range: 4.4 to 9.3 days, median: 5.5 days, (n = 8), r^2: range: 0.999 – 1.00 prothioconazole-desthio *(M04)*: $DT_{90}f$: range: 54.1 to 240 days, median: 140 days (n = 8), r2: range: 0.91 – 0.98 prothioconazole (normalised for 20°C; not normalised for moisture content): DT_{50} @20°C: range: 0.6 to 1.6 days, median: 1.3 days (n = 8), r2: range: 0.995 to 1.000. Geometric mean: 1.2 days, used for PELMOgw modelling. prothioconazole-desthio *(M04)* (normalised for 20°C; not normalised for moisture content): DT_{50} @20°C: range: 10.3 to 61.9 days, median: 22.05 days (n = 8), r2: range: 0.859 to 0.996. Geometric mean: 22.7 days, used for PELMOgw modelling. (57.1% conversion rate used for PELMOgw calculations
Soil accumulation and plateau concentration ‡	Not applicable (Soil accumulation testing is not necessary since $DT_{90}f$ values of prothioconazole and prothioconazole-desthio (M04) are less than one year.)

Soil adsorption/desorption (Annex IIA, point 7.1.2)

Active substance:

K_f /K_{oc} ‡	K_d and K_{oc} values of prothioconazole determined in aged column leaching studies due to the instability of the compound in standard batch equilibrium studies.
K_{oc} ‡	K_{oc}: 1765 mL/g (aged leaching study, only one soil tested, value used for PELMOgw modelling; 1/n set to 0.90)
K_d ‡	K_d: 15.2 mL/g (aged leaching study)
pH dependence ‡ (yes / no) (if yes type of dependence)	No information

Major metabolites:

Two major metabolites were performed during soil metabolism

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

Prothioconazole-S-methyl *(M01)*

K_{oc} K_d pH dependence (yes / no) (if yes type of dependence)	K_{foc}: Adsorption: 1974 – 2995 mL/g (n = 4), mean = 2556.3. Mean value used for PELMOgw modelling. Desorption: 2532 – 3359 mL/g (n = 4), mean = 2985.3 K_d: Adsorption: 15.6 – 64.1 mL/g (n = 4) Desorption: 20.0 – 71.9 mL/g (n = 4) 1/n: Adsorption: 0.85 – 0.91 (n=4), mean = 0.88. Mean value used for PELMOgw modelling. Desorption: 0.85 – 0.91 (n=4), mean = 0.88 No pH dependence

Prothioconazole-desthio *(M04)*

K_{oc} K_d pH dependence (yes / no) (if yes type of dependence)	K_{foc}: Adsorption: 523 – 625 mL/g (n = 4), mean = 575.4. Mean value used for PELMOgw modelling. Desorption: 562 – 876 mL/g (n = 4), mean = 687.2 K_d: Adsorption: 4.1 – 13.4 mL/g (n = 4) Desorption: 6.9 – 14.8 mL/g (n = 4) 1/n: Adsorption: 0.79 – 0.83 (n=4), mean = 0.81. Mean value used for PELMOgw modelling. Desorption: 0.77 – 0.84 mL/g (n=4), mean = 0.82 No pH dependence

Minor metabolite:

1,2,4-triazole (*M13*) (<2% AR in aerobic soil degradation studies)[18]

K_{foc} pH dependence (yes / no) (if yes type of dependence)	K_{foc}: Adsorption: 43 – 202 mL/g (n = 4), mean = 89 mL/g. 1/n: Adsorption: 0.827 – 1.016 (n=4), mean = 0.9155 mL/g. No pH dependence

[18] Values agreed following the discussion on triazole derivate metabolites during the experts' meeting PRAPeR 12 on fate and behaviour in January 2007.

‡ Endpoints identified by the 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 ‡	Guideline: SETAC (1995), BBA Part IV, 6-2 (1986) Precipitation: 200mm Time period: 2days Leachate: <1% AR; fractions not investigated
Aged residues leaching ‡	Guideline: US EPA 163-1 (1982) Aged for: 30 hours Precipitation: 1000 mL The total radioactivity in the leachate accounted for only 1.1% of the AR, and no individual leachate fraction resulted in a radioactivity content >0.2% of the AR. Therefore the leachate fractions were not analysed for parent compound or metabolites.
Lysimeter/ field leaching studies ‡	No data submitted, none required.

PEC (soil) (Annex IIIA, point 9.1.3)

Parent

Method of calculation	Soil density 1.5 g/ml, top 5 cm soil layer, 1st order DT_{50} (field) 2.8 days.
Application rate	Seed treatment (30 g a.s./ha, 0% interception) in combination with the use as spray application (3 times 200 g a.s./ha, 14 day intervals, 50%, 70% and 90% interception, respectively). Crop: wheat.

PECsoil for prothioconazole following sowing of treated seed

Days after sowing	PECsoil (mg/kg)
0	0.046
182	0.000

Subsequent PECsoil for prothioconazole following first foliar application (50% interception)

Days after 1st application	PECsoil (mg/kg)
0	0.133
14	0.004

Subsequent PECsoil for prothioconazole following second foliar application (70% interception)

Days after 2nd application	PECsoil (mg/kg)
0	0.084
14	0.003

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

Subsequent PECsoil for prothioconazole following third foliar application (90% interception)

Days after 3rd application	PECsoil (mg/kg)
0	0.030
1	0.023
2	0.018
4	0.011
7	0.005
14	0.001
28	0.000
50	0.000
100	0.000

Metabolite prothioconazole-desthio (*M04*)

Method of calculation	Soil density 1.5 g/ml, top 5 cm soil layer, 1st order DT_{50} (field) 72.3 days, 57.1% conversion (field), assumed no degradation between foliar applications (ie. applied simultaneously)
Application rate	Seed treatment (30 g a.s./ha) in combination with the use as spray application (3 times 200 g a.s./ha, 14 day intervals, 50%, 70% and 90% interception, respectively). Crop: wheat.

PECsoil for prothioconazole-desthio (M04) following sowing of treated seed

Days after sowing	PECsoil (mg/kg)
0	0.026
154	0.006

Subsequent PECsoil for prothioconazole-desthio (M04)
following three foliar applications applied 154 days after seed treatment
(50%, 70% and 90% interception, respectively)

Days after application	PECsoil (mg/kg)
0	0.143
1	0.142
2	0.140
4	0.138
7	0.134
14	0.125
28	0.109
50	0.089
100	0.055

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

Metabolite prothioconazole-S-methyl *(M01)*

Method of calculation	Soil density 1.5 g/cm3, top 5 cm soil layer, 1st order DT_{50} (lab) 46 days, 14.6% conversion (lab) at 7DAT, molecular weight correction x 1.041, assumed no degradation between foliar applications (ie. applied simultaneously).
Application rate	GAP: Seed treatment (30 g a.s./ha) in combination with the use as spray application (3 times 200 g a.s./ha, 14 day intervals, 50%, 70% and 90% interception, respectively. Interval between seed treatment and first spray = 182 days). Crop: wheat..

PECsoil for M01 following sowing of treated seed

Days after sowing	PECsoil (mg/kg)
7 (max. formation)	0.006
182	0.000

Subsequent PECsoil for M01 following three foliar applications applied 182 days after seed treatment (50%, 70% and 90% interception, respectively)

Days after application	PECsoil (mg/kg)
0	0.037
1	0.036
2	0.036
4	0.035
7	0.033
14	0.030
28	0.024
50	0.017
100	0.008

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

Hydrolysis of active substance and relevant metabolites (DT_{50}) ‡ (state pH and temperature)	prothioconazole: DT_{50} at 50°C: pH 9 and 7: > 1 year pH 4: 120 days DT_{50} at 25°C: pH 9, 7 and 4: > 1 year

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

Photolytic degradation of active substance and relevant metabolites ‡	**Aqueous photolysis study** (25°C, pH7): prothioconazole: phenyl label - DT_{50} = 44.3 hrs (R^2 = 0.999) triazole label - DT_{50} = 51.4 hrs (R^2 = 0.999) mean = 47.7 hours (n=2) predicted environmental half-life under solar summer conditions (June) of Phoenix, AZ, USA of 7.1 days and 11 days at Athens mineralisation at study end (18 days) = 3.0% AR (phenyl label), 0.5% AR (triazole label) Dark controls: prothioconazole was stable in the dark control samples, confirming that photolysis was the main process of degradation. %AR at 18 days was 108.7% for the phenyl label and 107.1% for the triazole label. prothioconazole-desthio (M04): max 55.7% AR 11 d prothioconazole-thiazocine (M12): max 14.1% AR, 5d 1,2,4-triazole (M13): max 11.9% AR, 18d **Quantum yield studies** prothioconazole: Quantum yields Φ of 0.0638 (pH 4) and 0.0047 (pH 9) were calculated. Environmental direct photolysis half-lives were in the range 50 to >200 days at pH 4 and 7 to 20 days at pH 9 for the periods of main use. prothioconazole-desthio *(M04)*: A quantum yield of Φ of 0.00449 was calculated. The resulting quantum yield and the UV absorption were used to estimate the environmental half-life of prothioconazole-desthio *(M04)* concerning direct photodegradation in water by two different simulation models (GC-SOLAR, half-life at 50^0 latitude and 0-1cm depth in the summer season: 269 days and Frank & Klöpffer, half-life at 50^0 latitude and 0-1cm depth > 1 year). 1,2,4-triazole *(M13)*: The UV-absorption data in the environmentally relevant pH range showed that 1,2,4-triazole *(M13)* dissolved in aqueous solution does not absorb any light at wavelengths above 290 nm.
Readily biodegradable (yes/no)	No data submitted, none required.

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

Degradation in water/sediment - DT_{50} water ‡	Aerobic lab sediment/water at 20°C DT_{50} water - 0.8 and 1.0 days, 1st Order (1.0 day value used for PECsw calculation) (1st Order, r^2 = 0.947 and 0.999, respectively, n = 2)
- DT_{90} water ‡	DT_{90} water - 2.7 and 3.4 days (1st Order, r^2 = 0.947 and 0.999, respectively, n = 2)
- DT_{50} whole system ‡	DT_{50} whole system - 2.8 and 1.6 days ('hockey stick', r^2 = 0.953 and 0.998, respectively, n = 2)
- DT_{90} whole system ‡	DT_{90} whole system - 76.4 and 23.6 days ('hockey stick', r^2 = 0.953 and 0.998, respectively, n = 2)
Mineralization	Hönniger Weiher: 14.7% AR at study end (121 days, phenyl-label). 1.9% AR at study end (121 days, triazole-label). Angler Weiher: 29.0% AR at study end (121 days, phenyl-label). 1.9% AR at study end (121 days, triazole-label).
Non-extractable residues	Hönniger Weiher: 50.8% AR at study end (121 days, phenyl-label). 52.5% AR at study end (121 days, triazole-label). Angler Weiher: 31.3% AR at study end (121 days, phenyl-label). 18.9% AR at study end (121 days, triazole-label).
Distribution in water / sediment systems (active substance) ‡	Sediment: phenyl-label: max 21.0 – 23.4 %AR, 1d (n=2) triazole-label: max 18.3 – 22.6 %AR, 1d (n=2)
Distribution in water / sediment systems (metabolites) ‡ Prothioconazole-desthio (M04)	Water layer: phenyl-label: max 13.9 – 32.3 %AR, 0- 7 d (n=2) triazole-label: max 9.2 – 31.9 %AR, 1 - d (n=2) Sediment: phenyl-label: max 21.9 – 26.9 %AR, 14 – 59 d (n=2) triazole-label: max 17.7 – 26.9 %AR, 14 – 59 d (n=2)
1,2,4-triazole (M13)	Water layer: triazole-label: max 0.8 – 37.2 %AR, 59 – 121 d (n=2)

‡ Endpoints identified by the 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	PECsw was estimated assuming spray drift from the maximum three recommended foliar applications. Scenario: water body of 30cm water depth with 5cm sediment, spray drift from a one hectare field. Calculations were performed for the active substance and metabolites prothioconazole-desthio (M04) and 1,2,4-triazole. For the metabolites, conversion rates of 32.3% and 37.2% respectively were assumed, with correction for molecular weight. Molecular weight of prothioconazole is 344.3 g/mol. Molecular weights of prothioconazole-desthio (M04) and 1,2,4-triazole (M13) 312.2 and 69.065 g/mol, respectively. DT_{50} of the active substance of 1.0 days used from water/sediment study. No DT_{50} values were available for the metabolites in the water phase. Spray drift values set based on the EC Guidance document 'Guidance Document on Aquatic Ecotoxicology' (Sanco/3268/2001), calculations performed for 1m and 5m distances. PECsw values were calculated both on a 90th percentile basis for a single application and a 77th percentile basis for three repeated applications at 14 day intervals.
Application rate	200 g active substance, applied three times per season
Main routes of entry	Spray drift

PECsw values for prothioconazole following one application, 90th percentile spray drift values

Days after appl'n	PECsw (µg/L) at 1m (2.77% spray drift)	PECsw (µg/L) at 5m (0.57% spray drift)
0	1.847	0.380
1	0.923	0.190
2	0.462	0.095
4	0.115	0.024
7	0.014	0.003
14	0.000	0.000
21	0.000	0.000
28	0.000	0.000
42	0.000	0.000

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

PECsw values for prothioconazole following three applications, 77th percentile spray drift values

Days after appl'n	PECsw (µg/L) at 1m (2.01% spray drift)	PECsw (µg/L) at 5m (0.41% spray drift)
0	1.340	0.273
1	0.670	0.137
2	0.335	0.068
4	0.084	0.017
7	0.010	0.002
14	0.000	0.000
21	0.000	0.000
28	0.000	0.000
42	0.000	0.000

Max PECsw values for metabolites prothioconazole-desthio and 1,2,4-triazole, three applications, 77th percentile spray drift

Metabolite	PECsw (µg/L) at 1m (2.01% spray drift)	PECsw (µg/L) at 5m (0.41% spray drift)
prothioconazole-desthio	1.177	0.240
1,2,4-triazole	0.300	0.061

PEC (sediment)

Parent

Method of calculation	No DT_{50} was available for the active substance or metabolites in sediment. Therefore, a worst case PECsed from spray drift was calculated assuming no degradation between foliar applications, using the same assumptions for the water body as used for PECsw. The calculations were performed using 77th percentile spray drift values and were repeated for 1m and 5m distance, assuming even distribution in 5cm depth of sediment and sediment density of 1.3 gcm^{-3}. In addition, a pseudo-PECsw for the active substance for use in the sediment dwelling organisms risk assessment was calculated assuming 77th percentile spray drift values (2.01% drift at 1m distance) with all three foliar application assumed to be applied simultaneously (i.e. 600 g a.s./ha). The resultant PECsed value was 4 µg/kg.
Application rate	200 g active substance, applied three times per season

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

Peak PECsed for prothioconazole and prothioconazole-desthio (M04) following foliar application at 200 g a.s./ha

Compound	peak PECsed (µg/kg) at 1m	peak PECsed (µg/kg) at 5m
Prothioconazole	4.342	0.886
prothioconazole-desthio	4.526	0.923

Compound	PECsed (µg/kg) at 1m, based on day 121 concentrations	PECsed (µg/kg) at 5m, based on day 121 concentrations
Prothioconazole	1.763	0.360
prothioconazole-desthio	1.867	0.381

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

Parent:

Method of calculation and type of study (*e.g.* modelling, monitoring, lysimeter)	FOCUS-PELMO (Version 1.1.1) for all 9 scenarios, according to all FOCUSgw guidance. Crop: wheat. DT_{50} a.s. 1.2 days (geometrically averaged 1st Order from field studies, normalised to 20°C). K_{oc} 1765 ml/g based on aged soil column leaching study. 1/n set at 0.9 (FOCUS recommended default in absence of measured data).
Application rate	Seed treatment (30 g a.s./ha, applied 11 Nov) in combination with the use as spray application (3 times 200 g a.s./ha – 50%, 50% and 70% crop interception, respectively, applied 10 Mar, 1 May, 1 July). Note interception factors for 2nd and 3rd applications more extreme worse-case than PECsoil calculations.

$PEC_{(gw)}$

Maximum concentration	Below 0.001 µg/L in nine different FOCUS scenarios
Average annual concentration (Results quoted for modelling with FOCUS gw scenarios, according to FOCUS guidance)	See above

Major metabolites:

Method of calculation and type of study (*e.g.* modelling, monitoring, lysimeter)	FOCUS-PELMO (Version 1.1.1) for all 9 scenarios, according to all FOCUSgw guidance. Crop: wheat.

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

Application rates	Prothioconazole-S-methyl *(M01)*: 14% (portion of the total degradation of prothioconazole determining its degradation to prothioconazole-S-methyl *(M01)*, based on laboratory trials). Mean K_{oc} of 2556.3 based on adsorption/desorption studies (n=4). Corresponding 1/n value – 0.88. DT_{50} 15.7 days (mean values from laboratory studies, n = 4) prothioconazole-desthio *(M04)*: 57% (portion of the total degradation of prothioconazole determining its degradation to prothioconazole-desthio *(M04)*, based on field dissipation trials). Mean K_{oc} of 575.4 based on adsorption/desorption studies (n=4). Corresponding 1/n value – 0.81. DT_{50} 22.7 days (geometrically averaged 1st Order from field studies, normalised to 20°C)

$PEC_{(gw)}$

Maximum concentration	Prothioconazole-S-methyl *(M01)*: below 0.001 µg/L in nine different FOCUS scenarios prothioconazole-desthio *(M04)*: below 0.001 µg/L in nine different FOCUS scenarios
Average annual concentration	See above

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

Direct photolysis in air ‡	Not studied – no data requested
Quantum yield of direct phototransformation	Not measured – no data requested
Photochemical oxidative degradation in air ‡	Prothioconazole: Half-life: 1.1 hours Chemical lifetime: 1.6 hours Calculated according to Atkinson (AOPWIN v. 1.87, 12 hour day, $1.5x10^6$ OH radicals/cm^3) prothioconazole-desthio *(M04)*: Half-life: 14.2 hours Chemical lifetime: 20.5 hours Calculated according to Atkinson (AOPWIN v. 1.87, 12 hour day, $1.5x10^6$ OH radicals/cm^3)
Volatilization ‡	Laboratory route and rate soil studies indicated that volatilisation of prothioconazole and prothioconazole-desthio (*M04*) is unlikely to take place because no volatiles were detected at levels above 0.1% AR.

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

PEC (air)

Method of calculation	Expert judgement based on vapour pressure (extrapolated: $<4x10^{-7}$ at 20^oC), Henry's Law Constant (3x10-5 $Pa.m^3.mol^{-1}$) and information on volatilisation..

$PEC_{(a)}$

Maximum concentration	Negligible

Definition of the Residue (Annex IIA, point 7.3)

Relevant to the environment	**Soil** For risk assessment: Prothioconazole, prothioconazole-S-methyl (M01) and prothioconazole-desthio (M04) For monitoring: prothioconazole
	Ground water For risk assessment: Prothioconazole, prothioconazole-S-methyl (M01) and prothioconazole-desthio (M04) For monitoring: Prothioconazole and prothioconazole-desthio (M04)
	Surface water For risk assessment Prothioconazole, prothioconazole-desthio (M04) and 1,2,4-triazole (M13) For monitoring: prothioconazole and prothioconazole-desthio (M04)
	Sediment For risk assessment Prothioconazole and prothioconazole-desthio (M04) For monitoring: Prothioconazole
	Air For risk assessment: Prothioconazole and prothioconazole-desthio (M04) For monitoring: prothioconazole and prothioconazole-desthio (M04)

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

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

Soil (indicate location and type of study)	No data provided – none requested
Surface water (indicate location and type of study)	No data provided – none requested
Ground water (indicate location and type of study)	No data provided – none requested
Air (indicate location and type of study)	No data provided – none requested

Classification and proposed labelling (Annex IIA, point 10)

with regard to fate and behaviour data	Possible candidate for R53 May cause long-term adverse effect to the aquatic environment

‡ Endpoints identified by the 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)

Effects on mammals ‡ (Annex IIIA, points 10.3)

Organism	Duration, Exposure	Test-substance	Ecotoxicological endpoint*
Rat	acute, oral	a.s.	$LD_{50(male, female)}$ > **6200 mg** a.s./kg bw/d
Rat	acute, oral	EC 250	$LD_{50(male, female)}$ > 2500 mg a.s./kg bw/d
Rat	acute, oral	FS 100	$LD_{50(male, female)}$ > 2500 mg a.s./kg bw/d
Rat	long-term (2-generation), gavage	a.s.	$NOEL_{parental}$ 9.7 mg a.s./kg bw/d $NOEL_{reproduction}$ **95.6 mg** a.s./kg bw/d
Rat	acute, oral	JAU 6476-desthio	$LD_{50(female)}$ 2506 mg p.m./kg bw/d $LD_{50(male)}$ 2806 mg p.m./kg bw/d
Mouse	acute, oral	JAU 6476-desthio	$LD_{50(female)}$ 3459 mg p.m./kg bw/d $LD_{50(male)}$ **2235 mg** p.m./kg bw/d
Rat	long-term (2-generation), oral	JAU 6476-desthio	$NOEL_{parental}$ 2.5 mg p.m./kg bw/d $NOEL_{reproduction}$ **10 mg** p.m./kg bw/d

(*) Values in bold are appropriate for use in risk assessment for wild mammals

Toxicity/exposure ratios for mammals (Annex IIIA, points 10.3)

Effects of the active substance of JAU 6476 EC 250 (spray application scenario)

Crop	Route of exposure	Target species(bw)	Time-scale	ETE*	Lowest TER	TER risk assessment trigger
Cereals	Exposure to residues on grass and cereal shoots	Small herbivorous mammal (<100 g)	acute	48.3 mg/kg bw	> 128	10
			long-term	67.2 ppm	11.9	5
Cereals	Exposure to residues on insects	Insectivorous mammal (<100 g)	acute	0.38 mg/kg bw	> 16000	10
			long-term	0.54 ppm	148	5
Cereals / Rape	Bio-accumulation fish	Fish eating mammal (>1000 g)	long-term	Fish BCF value < Annex VI trigger	NA	5
Cereals / Rape	Bio-accumulation earthworms	Earthworm eating mammal (<100 g)	long-term	a.s. not expected to bioaccumulate		5

* Estimated Theoretical Exposure, based on EPPO 1992 Vertebrate Scheme, assuming total dose (0.6 kg a.s./ha) applied as a single application with no degradation between treatments and 100% conversion from parent prothioconazole. (For insects, risk assessment based on residue levels on large insects following a single application of 200 g a.s./ha)

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

Effects of JAU 6476-desthio, metabolite of JAU 6476 (spray application scenario)

Crop	Route of exposure	Target species	Time-scale	ETE*	Lowest TER	TER risk assessment trigger
Cereals	Exposure to residues on grass and cereal shoots	Small herbivorous mammal (>100 g)	acute	48.3 mg/kg bw	> 46	10
			long-term	67.2 ppm	**2.38****	5

***** Estimated Theoretical Exposure, based on EPPO 1992 Vertebrate Scheme, assuming total dose (0.6 kg a.s./ha) applied as a single application with no degradation between treatments and 100% conversion from parent prothioconazole. (For insects residue levels based on a single application of 200 g a.s./ha)
****** Refined risk assessment using SANCO/4145/2000 25 September 2002 (based on measured residues in green parts of cereals and a mean DT_{50} from 8 residue trials) results in TERlt of 7.2 (note that Table 9.24 in Volume III Section B.9.3.2.1) contains an error in that the MAF should be 1.5 and not 1.05 as stated in the table, corrected ETE is 0.533 mg /kg diet

Effects of the active substance of JAU 6476 FS 100 (seed treatment scenario)

Route of exposure	target species (bw)	Time-scale	ETE*	TER	TER risk assessment trigger
Exposure to dressed seeds	Granivorous mammal (<100 g)	acute	45	>137	10
	Granivorous mammal (<100 g)	long-term	150 ppm	5.3**	5

* Estimated Theoretical Exposure assuming 30% food consumption and 150 mg a.s./kg seed and no conversion for wet weight (i.e. assumed to equivalent to normal bird diet)
** Refined by using maximum mean daily level on treated seed remaining on soil surface averaged over 0 to 9 day exposure and normalised to a use rate of 15 g a.s./100 kg seed (3 field trials). TER=1.7 calculated by EFSA in accordance with SANCO/4145/2000

Due to the lower application rate/ha for the seed treatment, all other potential routes of exposure are covered by the risk assessment presented for the foliar use

Effects of JAU 6476-desthio, metabolite of JAU 6476 (seed treatment scenario)

Route of exposure	Target species	Time-scale	ETE*	Lowest TER	TER risk assessment trigger
Exposure to dressed seeds	Small granivorous mammal (>100 g)	acute	7.5 mg/kg bw	> 46	10
		long-term	25.05 ppm	6.4	5

* Estimated Theoretical Exposure assuming 30% food consumption and mean daily measured residue of 25.05 mg desthio/kg seed and no conversion for wet weight (i.e. assumed to equivalent to normal bird diet)
Due to the lower application rate/ha for the seed treatment, all other potential routes of exposure are covered by the risk assessment presented for the foliar use

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

Effects on birds ‡ (Annex IIA, point 8.1, Annex IIIA, points 10.1)

Organisms	Duration	Test-substance	Ecotoxicological endpoint*	
Bobwhite quail	Acute	a.s.	LD_{50}	**> 2000 mg a.s./kg bw**
Bobwhite quail	5 d dietary	a.s.	LC_{50} calc. LD_{50}	**> 5000 mg a.s./kg diet** > 1413 mg a.s./ kg bw/day
Mallard duck	5 d dietary	a.s.	LC_{50} calc. LD_{50}	> 5000 mg a.s./kg diet > 2457 mg a.s./kg bw/day
Bobwhite quail	Reproduction 22 w dietary	a.s.	NOEC calc. NOEL	≥ 1000 mg a.s./kg diet ≥ 86 mg a.s./kg bw/day
Mallard duck	Reproduction 21 w dietary	a.s.	NOEC calc. NOEL	**700 mg a.s./kg diet** 78 mg a.s./kg bw/day
Bobwhite quail	Acute	JAU 6476-desthio	LD_{50}	**> 2000 mg p.m./kg b.w.**
Bobwhite quail	5 d dietary	JAU 6476-desthio	LC_{50} calc. LD_{50}[1]	**4090 mg p.m./kg diet** > 297 mg p.m./kg bw/d
Bobwhite quail	Reproduction 20 w dietary	JAU 6476-desthio	NOEC calc. NOEL	**173 mg p.m./kg diet** 14.8 mg p.m./kg bw/day
Mallard duck	Reproduction 20 w dietary	JAU 6476-desthio	NOEC calc. NOEL	≥ 500 mg p.m./kg diet 63 mg p.m./kg bw/day

(*) Bold values are relevant for risk assessment
[1] value represents the dose converted from the test group in which No Effect on mortality or food consumption was reported (1243 mg/kg diet/d multiplied by the mean daily food consumption (6.4 g/d for the 5 day exposure period) divided by the mean bodyweight (26.75 g for the 5 day exposure period). A more precise conversion of the LC_{50} value requires reanalysis of data using the converted daily dietary doses for each test group.

Toxicity/exposure ratios for birds (Annex IIIA, point 10.1)

Effects of the active substance of JAU 6476 EC 250 (spray application scenario)

Crop	Route of exposure	Target species	Time-scale	ETE*	Lowest TER	TER risk assessment trigger
Cereals	Exposure to residues on grass and cereal shoots	Large herbivorous bird (>100 g)	acute	16.13 mg/kg bw	> 124	10
			short-term	67.2 ppm	> 74	10
			long-term	67.2 ppm	10.4	5
Rape	Exposure to residues on non-grass herbs	Large herbivorous bird (>100 g)	acute	2.60 mg/kg bw	> 769	10
			short-term	10.85 ppm	> 461	10
			long-term	10.85	64.5	5

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

Crop	Route of exposure	Target species	Time-scale	ETE*	Lowest TER	TER risk assessment trigger
Cereals	Exposure to residues on insects	Insectivorous bird (<100 g)	acute	4.17 mg/kg bw	> 480	10
			short-term	5.8 ppm	> 862	10
			long-term	5.8 ppm	Long term exposure unlikely	5
Cereals / Rape	Bio-accumulation fish	Fish eating bird (>100 g)	long-term	Fish BCF value < Annex VI trigger	NA	5
Cereals / Rape	Bio-accumulation earthworms	Earthworm eating bird (<100 g)	long-term	a.s.. not expected to bioaccumulate	NA	5

***** Estimated Theoretical Exposure, based on EPPO 1992 Vertebrate Scheme, assuming total dose (0.6 kg a.s./ha) applied as a single application with no degradation between treatments. (For insects risk assessment is based on predicted levels in small insects for a single application of 200 g a.s./ha)

Effects of JAU 6476-desthio, metabolite of JAU 6476 (spray application scenario)

Crop	Route of exposure	Target species	Time-scale	ETE*	Lowest TER	TER risk assessment trigger
Cereals	Exposure to residues on grass and cereal shoots	Large herbivorous bird (>100 g)	acute	16.13 mg/kg bw	> 121	10
			short-term	67.2 ppm	> 61	10
			long-term	67.2 ppm	**2.5****	5
Rape	Exposure to residues on non-grass herbs	Large herbivorous bird (>100 g)	acute	2.60 mg/kg bw	Covered by cereal assessment	10
			short-term	10.85 ppm	Covered by cereal assessment	10
			long-term	10.85	15.9	5
Cereals	Exposure to residues on insects	Insectivorous bird (<100 g)	acute	4.17 mg/kg bw	Covered by herbivorous bird cereal assessment	10
			short-term	5.8 ppm	Covered by herbivorous bird cereal assessment	10
			long-term	5.8 ppm	29.8	5

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

Crop	Route of exposure	Target species	Time-scale	ETE*	Lowest TER	TER risk assessment trigger
Cereals / Rape	Bio-accumulation fish	Fish eating bird (>100 g)	long-term	Fish BCF value < Annex VI trigger	NA	5
Cereals / Rape	Bio-accumulation earthworms	Earthworm eating bird (<100 g)	long-term	a.s. not expected to bioaccumulate	NA	5

***** Estimated Theoretical Exposure, based on EPPO 1992 Vertebrate Scheme, assuming total dose (0.6 kg a.s./ha) applied as a single application with no degradation between treatments and 100% conversion from parent prothioconazole. (For insects residue levels based on a single application of 200 g a.s./ha)
****** Refined risk assessment using SANCO/4145/2000 25 September 2002 (based on measured residues in green parts of cereals and a mean DT_{50} from 8 residue trials) results in TERlt of 27.8 (note that Table 9.11 in Volume III Section B.9.1.4.1 b)) contains an error in that the MAF should be 1.5 and not 1.05 as stated in the table, corrected ETE is 0.533 mg /kg diet

Effects of the active substance of JAU 6476 FS 100 (seed treatment scenario)

Route of exposure	Target species (bw)	Time-scale	ETE	TER	TER risk assessment trigger
Exposure to dressed seeds	Granivorous birds (<100 g)	acute	45 mg/kg bw*****	> 44	10
	Granivorous birds (<100 g)	short-term	150 ppm	> 33	10
	Granivorous birds (<100 g)	long-term	150 ppm	4.6**	5

* Estimated Theoretical Exposure based on dry wt food intake as % bw consumed per day x predicted residue level (150 mg a.s./kg seed)
**Rapid decline of residues reported in field studies, combined with short germination period indicate long term exposure is unlikely to pose significant risk to bird populations. TER= 1.37 calculated by EFSA in accordance with SANCO/4145/2000.

Effects of JAU 6476-desthio, metabolite of JAU 6476 (seed treatment scenario)

Route of exposure	Target species (bw)	Time-scale	ETE	TER	TER risk assessment trigger
Exposure to dressed seeds	Granivorous birds (<100 g)	acute	7.15 mg/kg bw*****	> 279	10
	Granivorous birds (<100 g)	short-term	25 ppm	>163	10
	Granivorous birds (<100 g)	long-term	25 ppm	6.9**	5

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

* Estimated Theoretical Exposure based on dry wt food intake as % bw consumed per day x measured residue level (25.05 mg/kg seed)
** Refined by using maximum mean daily level on treated seed remaining on soil surface averaged over 0 to 9 day exposure and normalised to a use rate of 15 g a.s./100 kg seed (3 field trials). TER=1.6 calculated by EFSA in accordance with SANCO/4145/2000.

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

JAU 6476 and EC250 formulation

Target species / Test substance	Time-scale	Toxicological Endpoint	TER	TER risk assessment trigger	Result of refined risk assessment
Fish					
Oncorhynchus mykiss, a.s.	acute	LC_{50} 1.83 mg a.s./L	994[1]	100	not necessary
Oncorhynchus mykiss, EC 250	acute	LC_{50} 1.00 mg a.s./L	543[1]	100	not necessary
Lepomis macrochirus, a.s.	acute	LC_{50} 4.59 mg a.s./L	2494[1]	100	not necessary
Cyprinus carpio, a.s.	Acute	LC_{50} 6.91 mg a.s./L	3839[1]	100	not necessary
Cyprinus carpio, EC 250	Acute	LC_{50} 3.72 mg a.s./L	2067[1]	100	not necessary
Oncorhynchus mykiss (ELS), a.s.	Chronic	NOEC 0.308 mg a.s./L	**167**[1]	**10**	not necessary
Daphnia					
Daphnia magna, a.s.	Acute	EC_{50} 1.3 mg a.s./L	**722**[1]	**100**	not necessary
Daphnia magna, EC 250	Acute	EC_{50} 0.71 mg a.s./L	**394**[1]	**100**	not necessary
Daphnia magna, a.s.	Chronic	NOEC 0.56 mg a.s./L	**304**[1]	**10**	not necessary
Freshwater Algae					
Pseudokirchneriella subcapitata, a.s.	Sub-chronic	E_bC_{50} 1.10 mg a.s./L E_rC_{50} 2.18 mg a.s./L	598[1] 1185[1]	**10**	not necessary
Pseudokirchneriella subcapitata, EC250	Sub-chronic	E_bC_{50} 2.92 mg a.s./L ErC_{50} 1.11 mg a.s./L	1587[1] 603[1]	**10**	not necessary
Sediment organisms					
Chironomus riparius a.s.	Chronic	NOEC 9.14 mg a.s./L	**4967**[1]	**10**	not necessary
Fish, Bioconcentration					
Lepomis macrochirus	BCF_{parent}		19.7		not necessary
	Clearance time (CT_{50} days): 0.8				
	Level of residues (%) after 14 day depuration phase: 9%				

[1] Based on a PEC of 0.00184 mg a.s./L (single application @ 200 g a.s./ha cereals, using SANCO/3628/2001 drift values)

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

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

Consideration of effects of metabolites of JAU 6476 on aquatic organisms

JAU 6476-desthio

Target species	Time-scale	Toxicological Endpoint		TER	TER risk assessment trigger	Result of refined risk assessment
Fish						
Oncorhynchus mykiss	Acute	LC_{50}	6.63 mg p.m./L	5666	100	Not necessary
Leuciscus idus melanotus	Acute	LC_{50}	13.2 mg p.m./L	11282[1]	100	Not necessary
Oncorhynchus mykiss (ELS)	Chronic	NOEC	3.34 µg p.m./L	**2.9**[1]	10	TER = 14.1[2]
Daphnia						
Daphnia magna	Acute	EC_{50}	> 10 mg p.m./L	>8547[1]	100	Not necessary
Daphnia magna	Chronic	NOEC	0.10 mg p.m./L	85.4[1]	10	Not necessary
Freshwater Algae						
Scenedesmus subspicatus	Sub-chronic	E_bC_{50} E_rC_{50}	0.073 mg p.m./L 0.55 mg p.m/L	59.8[1] 470[1]	10	Not necessary
Sediment organisms						
Chironomus riparius	Chronic	NOEC	2.0 mg p.m./L	2564[1]	10	Not necessary
Fish, Bioconcentration						
Lepomis macrochirus	BCF_{parent} 65					Not necessary
	Clearance time (CT_{50} days): 0.4-05					
	Level of residues (%) after 14 day depuration phase: 4%					

[1] Based on PEC of 0.00117 mg/L (3 @ 200 g a.s./ha, spray drift at 1 m distance using SANCO/3628/2001 drift values)
[2] Based of PEC at 5 m distance (0.00024 mg/L)

JAU 6476-S-methyl

Target species	Time-scale	Toxicological Endpoint		TER	TER risk assessment trigger	Result of refined risk assessment
Fish						
Oncorhynchus mykiss	acute	LC_{50}	1.8 mg p.m./L	Not required[1]	100	Not necessary
Daphnia						
Daphnia magna	acute	EC_{50}	2.8 mg p.m./L	Not required[1]	100	Not necessary

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

Target species	Time-scale	Toxicological Endpoint	TER	TER risk assessment trigger	Result of refined risk assessment
Freshwater Algae					
Pseudokirchneriella subcapitata	sub-chronic	E_bC_{50} 3.77 mg p.m./L E_rC_{50} 47.4 mg p.m./L	Not required[1]	10	Not necessary

[1] TER values not calculated since JAU 6476-S-methyl was not identified as a major metabolite in fate & behaviour section.

1,2,4-Triazole

Target species	Time-scale	Toxicological Endpoint	TER	TER risk assessment trigger	Result of refined risk assessment
Fish					
Oncorhynchus mykiss	acute	LC_{50} 498 mg p.m./L	1660000[1]	100	Not necessary
Oncorhynchus mykiss	chronic	NOE_rC 3.2 mg a.s./L	10666[1]	10	Not necessary
Daphnia					
Daphnia magna	acute	EC_{50} 900 mg p.m./L	3000000[1]	100	Not necessary
Freshwater Algae					
Pseudokirchneriella subcapitata	sub-chronic	E_bC_{50} 8.2 mg p.m./L* E_rC_{50} 22.5 mg p.m./L*	27333[1] 75000[1]	10	Not necessary

[1] Based on initial PEC of 0.0003 mg/L (3 @ 200 g a.s./ha, cereals at 1 m distance using SANCO/3628/2001 drift values)
* Endpoint value according to agreement in PRAPeR expert meeting on triazole metabolites (PRAPeR 13, January 2007).

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

Time-scale	Species / Formulation	Endpoint	Q_{HO}, Q_{HC} (crop)	Q_{HO}, Q_{HC} Trigger value	Result of refined risk assessment
acute (oral)	*Apis mellifera* a.s.	LD_{50} > 71 µg a.s./bee	2.8	50	Not necessary
acute (contact)	*Apis mellifera* a.s.	LD_{50} > 200 µg a.s./bee	1.0	50	Not necessary
acute (oral)	*Apis mellifera* EC 250	LD_{50} > 48.7 µg a.s./bee	4.1 (cereals)	50	Not necessary
acute (contact)	*Apis mellifera* EC 250	LD_{50} > 200 µg a.s./bee	1 (cereals)	50	Not necessary

Maximum application rate in cereals (200 g a.s./ha) is greater than for oilseed rape, therefore due to low HQ values a separate risk assessment is not required for oilseed rape

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

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

Species	Stage	Test sub-stance	Exposure, Application rate	Results	Outcome of the risk assessment (RA)
Predatory mites					
Typhlodromus pyri	larvae / adults	EC 250	Lab., coffin cells, 14 d 2 g a.s./ha 3.5 g a.s./ha 6.25 g a.s./ha 11 g a.s./ha 20 g a.s./ha	LR_{50} = 18.7 g a.s./ha corrected Mortality [%] / Effect on Repro. [%] 11.2 / 4 18.5 / -14 4.0 / -6 27.5* / 19 52.9* / n.a. [1)]	No adverse effects to be expected in the off-crop area. Higher tier study required for the in-crop area.
Typhlodromus pyri	larvae / adults	EC 250	Ext. lab., bean leaves, 14 d 100 g a.s./ha 157 g a.s./ha 245 g a.s./ha 380 g a.s./ha 600 g a.s./ha	LR_{50} = 445.5 g a.s./ha corrected Mortality [%] / Effect on Repro. [%] -2.3 / 14 1.5 / 9 9.1 / 47* 45.1* / 40* 67.8* / n.a. [a)]	No adverse effects to be expected in the off- and in the in-crop area.
Typhlodromus pyri	larvae / adults	EC 250	Ext. lab., aged residues, bean leaves, 300 g a.s./ha, exposure 14 d (each test) Test started 1 day after appl. Test started 15 days after appl.	Corrected Mortality [%] / Effect on Repro [%] 14.5 / 7.5 6.4 / -28.8	No adverse effects to be expected in the off- and in the in-crop area.

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

Species	Stage	Test sub-stance	Exposure, Application rate	Results	Outcome of the risk assessment (RA)
Parasitoids					
Aphidius rhopalosiphi	adults	EC 250	Lab., glass plates, 14 d 1st run: 2 g a.s./ha 6.3 g a.s./ha 20 g a.s./ha 63 g a.s./ha 200 g a.s./ha 2nd run: 63 g a.s./ha 84 g a.s./ha 112 g a.s./ha 150 g a.s./ha 200 g a.s./ha	LR_{50} = 139.9 g a.s./ha Corrected Mortality [%] / Effect on Repro. [%] 1st run: 3.5 / 21 6.9 / 10 3.5 / 39 3.5 / 34 100.0 / n.a. a) 2nd run: 13.3 / 17 13.3 / 36 33.3* / 44* 33.3* / 53* 96.7* / n.a. a)	No adverse effects to be expected in the off-crop area. According to the refined risk assessment, no adverse effects are to be expected in the in-crop area.
Aphidius rhopalosiphi	adults	EC 250	Ext. lab., wheat plants, Control 17 g a.s./ha 45 g a.s./ha 115 g a.s./ha 300 g a.s./ha 600 g a.s./ha	48 h mortality <5% in any of test concentrations. No significant effect on reproduction in any treatment	No adverse effects in the off-crop or in the in-crop area

a) not assessed due to mortality > 50 % at this concentration
* significantly different from control (t-test p <0.05)

Species	Stage	Test sub-stance	Exposure, Application rate	Results	Outcome of the risk assessment (RA)
Foliage dwelling predators					
Coccinella septempunctata	larvae	EC 250	EC 250 Lab., glass plates, 46 d control 25 g a.s./ha 50 g a.s./ha 97.5 g a.s./ha 180 g a.s./ha 375 g a.s./ha	LR_{50} = 229.8 g a.s./ha corrected Mortality [%] / Larvae per egg laying female – / 147 -9.6 / 54 -5.3 / 0 25.4 / 84 30.7 / 549 73.7* / n.a. a) effects on reproduction are not considered to be treatment related (no adverse effects on reproduction at the highest tested treatment rate).	No adverse effects to be expected in the off-crop area. According to the refined risk assessment, no adverse effects are to be expected in the in-crop area.

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

Species	Stage	Test sub-stance	Exposure, Application rate	Results	Outcome of the risk assessment (RA)
Chrysoperla carnea	larvae	EC 250	Lab. glass plates, 23 d 200 g a.s./ha 400 g a.s./ha 600 g a.s./ha	Corrected Mortality [%] 15.2* 28.3* 41.3* no adverse effects on reproduction	No adverse effects to be expected in the off- and in the in-crop area.

a) not assessed due to mortality > 50 % at this concentration
* significantly different from control (t-test p <0.05)

Species	Stage	Test sub-stance	Exposure, Application rate	Results	Outcome of the risk assessment (RA)
Ground dwelling predators					
Poecilus cupreus	adults	EC 250	Quartz sand, 14 d 400 g a.s./ha 600 g a.s./ha	corrected Mortality [%] 0.0 3.3 no adverse effect on feeding rate	No adverse effects to be expected in the off- and in the in-crop area.
Aleochara bilineata	adults / larvae	EC 250	Quartz sand, 87 d 42 g a.s./ha 200 g a.s./ha 400 g a.s./ha	Effect on reproduction [%] 2.5 9.9 24.6*	No adverse effects to be expected in the off- and in the in-crop area.
Poecilus cupreus	adults	FS 100	FS 100, ext. lab., 14 d, soil (Lufa 2.1), dressed seeds, 22.47 g a.s./ha	corrected Mortality [%] 0 Effect on feeding rate [%] 5.6 - 9.6	No adverse effects to be expected
Aleochara bilineata	adults / larvae	FS 100	FS 100, ext. lab., 82 d, soil (Lufa 2.1), dressed seeds, 19.34 g a.s./ha	Effect on reproduction [%] 11.2	No adverse effects to be expected
Pardosa spp.	adults	FS 100	FS 100, ext. Lab., 14 d, soil (Lufa 2.1), dressed seeds, 22.3 g a.s./ha	corrected Mortality [%] -3.1 Effect on feeding rate [%] -18	No adverse effects to be expected

* significantly different from control (t-test p <0.05)

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

Hazard quotients (HQ) for the two standard ESCORT II indicator species at Tier I

(based on single maximum foliar application of 200 g a.s./ha and a MAF value of 1)

Species	Exposure (g a.s./ha)	LR_{50} (g a.s./ha)	HQ (exposure/toxicity)
In-field			
T pyri	200	18.7	**10.7**
A rhopalosiphi	200	139.9	1.4
Off-field			
T pyri	5.54	18.7	0.3
A rhopalosiphi	5.54	139.9	0.04

Value in **bold** is above the trigger value of 2. Risk assessment refined using higher tier data - see above

Effects on earthworms and other non-target macro-organisms (Annex IIA, point 8.4 and point 8.6, Annex IIIA, point 10.6)

Effects on earthworms, JAU 6476 EC 250 (spray application scenario)

Species	Tested formu-lation	Time-scale	Endpoint [mg a.s./kg d.wt.s.]	TERcorr1, 2 (Peat cont. in soil)	TER risk assessment trigger	Result of refined risk assessment
Eisenia foetida	a.s.	acute	LC_{50} > 1000	> 3759 (10%)	10	Refined risk assessment not necessary
Eisenia foetida	EC 250	acute	LC_{50} > 249.3	> 937 (10%)	10	Refined risk assessment not necessary
Eisenia foetida	EC 250	long-term	NOEC 1.33 (1000 g a.s./ha)	5.0 (10%)	5	No adverse effects to be expected, see results of the field study.
Lumbricius terrestris, *L. rubellus*, *L. castanea*, *Aporrectodea caliginosa*, *A. terrestris longa*	EC 250	field study (grassland site)	3 × 200 g a.s./ha 5 different species identified and assessed. 46% reduction in the number of *A caliginosa* juveniles 7 weeks after first application (2 weeks after final application). No adverse effect 5 month after first application. (Maximum measured soil PEC 0.052 mg prothioconazole/kg based on soil sampling depth of 10 cm which is equivalent to a soil PEC of 0.104 mg prothioconazole/kg over the standard 5 cm depth)		1	No further refinement necessary

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

[1] using toxicity values adjusted by a factor of 2 to correct for the lipophilic character of the test substance (log P_{ow} > 2) and the high organic matter content (peat) of 10 % in the test substrate.
[2] based on maximum PEC of 0.133 mg prothioconazole/kg soil (200 g a.s./ha cereals)

Effects on other soil non-target macro-organisms, JAU 6476 EC 250 (spray application scenario)

Species	Tested Formulation Time-scale	Endpoint [mg a.s./kg d.wt.s.]	TER3 (Peat cont. in soil)	TER risk assessment trigger	Result of refined risk assessment
Folsomia candida	a.s. long-term	NOEC 64	240[1] (10%)	5	Refined risk assessment not necessary
Hypoaspis aculeifer	a.s. long-term	NOEC 100	1250 (soil) [2)]	5	Refined risk assessment not necessary

[1] using toxicity values adjusted by a factor of 2 to correct for the lipophilic character of the test substance (log Pow > 2) and the high organic matter content (peat) of 10 % in the test substrate.
[2] Lufa 2.1 soil, ca. 0.9 % organic carbon therefore no need to correct toxicity endpoint
[3] based on maximum PEC of 0.133 mg a.s./kg soil (200 g a.s./ha cereals)

Soil litter degradation study (combined spray application and seed treatment scenario)

Type of study	Time scale	Test-substance	Ecotoxicological endpoint: [%] field soil litter degradation	Result of refined risk assessment
Field Soil Litter Degradation	126 days	FS 100 (23.2 g a.s./ha) followed by JAU 6476 EC 250 (3 @ 200 g a.s./ha during 26 day period)	**after 34 days**: test item: 51.7; control: 52.1 **after 95 days**: test item: 74.3; control: 78.4 **after 126 days** test item: 92.0; control 91.2	Not necessary

Consideration of effects of metabolites of JAU 6476 (spray application scenario)

Effects of metabolites on earthworms (combined spray application and seed treatment scenario)

Species	Test substance	Time-scale	Endpoint [mg p.m./kg d.wt.s.]	TER Peat cont. in soil	TER risk assessment trigger	Result of refined risk assessment
Eisenia fetida	JAU 6476-desthio	acute	LC_{50}> 1000	> 3496 [1, 2] 10%	10	Not necessary

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

Species	Test substance	Time-scale	Endpoint [mg p.m./kg d.wt.s.]	TER Peat cont. in soil	TER risk assessment trigger	Result of refined risk assessment
Eisenia foetida	JAU 6476-desthio	long-term	NOEC 1[3]	3.5 [1, 2] 10%	5	No adverse effects to be expected, see results of the field study. Desthio-metabolite confirmed as being present in field study: maximum concentration recorded 7 days after second application, was 0.106 mg/kg which is equivalent to 0.212 mg desthio/kg over the standard 5 cm depth.
Eisenia foetida	JAU 6476-S-methyl	acute	LC_{50}> 1000	>13513 [1,2] 10 %	10	Not necessary
Eisenia foetida	JAU 6476-S-methyl	long-term	NOEC 100	1352 [1,2] 10%	5	Not necessary

[1] using toxicity values adjusted by a factor of 2 to correct for the lipophilic character of the test substance (log P_{ow} > 2) and the high organic matter content (peat) of 10 % in the test substrate.
[2] based on maximum PEC of 0.143 mg desthio/kg soil and 0.037 mg MO1/ kg soil (assuming 3 @ 200 g a.s./ha plus seed treatment (cereals))
[3] Number of juveniles in control (19) less than the required number (30). Absence of a steep dose response over the 320-fold range of concentrations tested provides a weight of evidence that absolute NOEC would not differ greatly from that proposed (mid range of concentrations tested)

Effects of metabolites on other soil non-target macro-organisms (combined spray application and seed treatment scenario)

Species	Test substance	Time-scale	Endpoint [mg a.s./kg d.wt.s.]	TER1, 2 (Peat cont. in soil)	TER risk assessment trigger	Result of refined risk assessment
Folsomia candida	JAU 6476-desthio	long-term	NOEC 62.5	218 10%	5	Not necessary
Folsomia candida	JAU 6476-S-methyl	long-term	NOEC 31.6	427 10%	5	Not necessary

[1] using toxicity values adjusted by a factor of 2 to correct for the lipophilic character of the test substance (log P_{ow} > 2) and the high organic matter content (peat) of 10 % in the test substrate.
[2] based on maximum PEC of 0.082 mg desthio/kg soil and 0.037 mg MO1/ kg soil (assuming 3 @ 200 g a.s./ha plus seed treatment (cereals))

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

Risk assessment for earthworms and other soil macro organisms from the proposed use of JAU 6476 FS 100 (seed treatment)

The following studies were conducted using the seed treatment formulation (JAU 6476 FS 100).

Effects on earthworms, JAU 6476 FS 100 (seed treatment scenario)

Species	Tested Formulation Time-scale	NOEC [mg a.s./kg d.wt.s.]	TER Peat cont. in soil	TER risk assessment trigger	Outcome of the RA (risk assessment)
Range of species in an arable field study	FS 100 long-term	1150 kg seeds/ha (10 g a.s./dt seeds) equivalent to 122 g a.s./ha	**1.77**[1, 2] 10 %	5	No significant lasting effects reported in a field study following 3 spray applications each of 200g a.s./ha.
Folsomia candida [3]	FS 100 long-term	230 kg seeds/ha (10 g a.s./dt seeds) equivalent to 24.38 g a.s./ha	**0.35**[1, 5] 10 %	5	Higher tier study conducted (see next line)
Folsomia candida [4]	FS 100 long-term	1150 kg seeds/ha (10 g a.s./dt seeds) equivalent to 112 g a.s./ha	**3.25** 5 %	5	No evidence of any treatment related impact on reproductive performance at maximum concentration tested. No evidence of long term impact on organic matter breakdown reported in a litter bag study following application of FS 100 at 23 g a.s./ha followed by 3 spray applications each of 200 g a.s./ha.

[1] using toxicity values adjusted by a factor of 2 to correct for the lipophilic character of the test substance (log P_{ow} > 2) and the high organic matter content (peat) of 10 % in the test substrate.
[2] based on a comparison of the adjusted NOEC (61 g a.s./ha) and proposed application rate of 34.5 g a.s./ha
[3] Soil depth 1.3 cm in the test unit, seeds in 0.5 cm soil depth
[4] Soil depth 5 cm in the test unit, seeds in 2.5 cm soil depth
[5] based on a comparison of the adjusted NOEC (12.19 g a.s./ha) and proposed application rate of 34.5 g a.s./ha

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

JAU 6476 a.s.

Type of study	Duration	Endpoint / Outcome		Result of refined risk assessment
C-cycle	28 d	2.0 kg a.s./ha	no influence	not necessary
N-cycle	28 d	2.0 kg a.s./ha	no influence	not necessary

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

Consideration of effects of metabolites of JAU 6476 on soil non-target micro-organisms

JAU 6476-desthio

Type of study	Duration	Endpoint / Outcome		Result of refined risk assessment
N-cycle	28 d	0.2 kg p.m./ha	no influence	not necessary
N-cycle	28 d	1.0 kg p.m./ha	no influence	not necessary

JAU 6476-S-methyl

Type of study	Duration	Endpoint / Outcome		Result of refined risk assessment
C-cycle	28 d	2.0 kg p.m./ha	no influence	not necessary
N-cycle	28 d	2.0 kg p.m./ha	no influence	not necessary

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

Effects of JAU 6476 on non-target terrestrial plants

Type of test	Test substance	Most sensitive species	Tested application rate	Max. phytotoxic effect [%]	Result of refined risk assessment
Pre-emergence	JAU 6476 a.s.	*Amaranthus retroflexus*	200 g a.s./ha	5	not necessary
Post-emergence		*Amaranthus retroflexus, Beta vulgaris*	250 g a.s./ha	10	not necessary
Pre-emergence	JAU 6476 EC 250	*Amaranthus retroflexus*	200 g a.s./ha	5	not necessary
Post-emergence		-	250 g a.s./ha	0	not necessary

Classification and proposed labelling (Annex IIA, point 10)

with regard to ecotoxicologal data	R51/53	Toxic to aquatic organisms, may cause long-term adverse effect to the aquatic environment

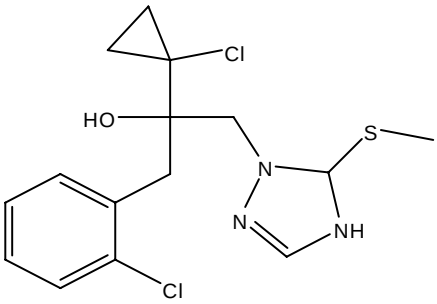
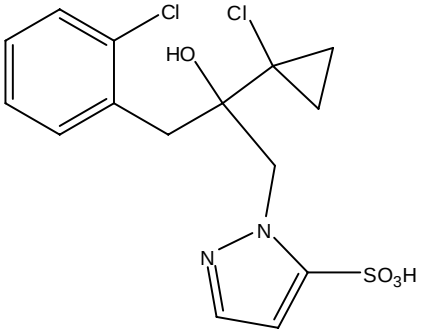
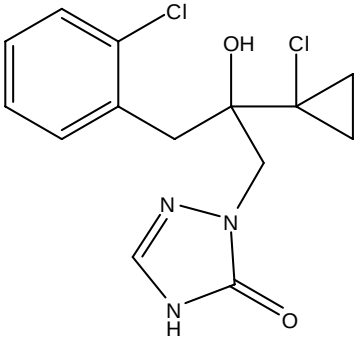
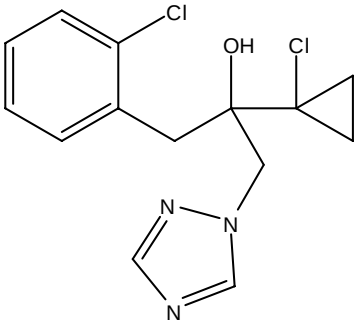
‡ Endpoints identified by the EU-Commission as relevant for Member States when applying the Uniform Principles

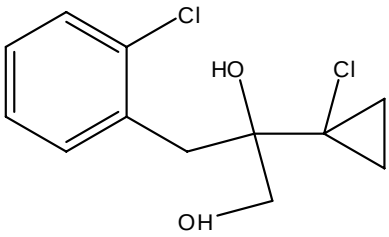
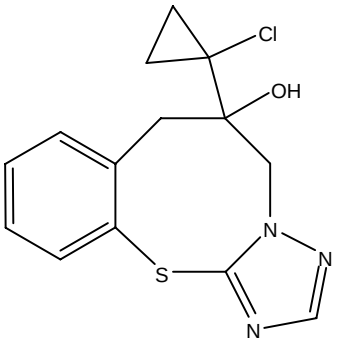
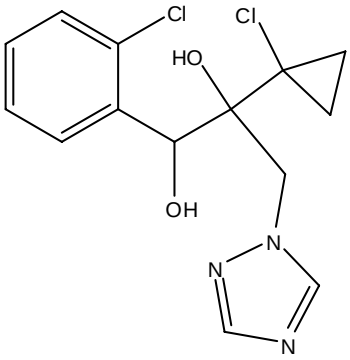
APPENDIX 2 – ABBREVIATIONS USED IN THE LIST OF ENDPOINTS

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
EU	European Union
FAO	Food and Agriculture Organisation of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	good agricultural practice
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GS	growth stage
h	hour(s)
ha	hectare
hL	hectolitre
HPLC	high pressure liquid chromatography or high performance liquid chromatography
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
K_{oc}	organic carbon adsorption coefficient
L	litre
LC	liquid chromatography
LC-MS	liquid chromatography-mass spectrometry
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LC_{50}	lethal concentration, median

LD_{50}	lethal dose, median; dosis letalis media
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantification (determination)
µg	microgram
mN	milli-Newton
MRL	maximum residue limit or level
MS	mass spectrometry
NESTI	national estimated short term intake
NIR	near-infrared-(spectroscopy)
nm	nanometer
NOAEL	no observed adverse effect level
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

APPENDIX 3 – USED COMPOUND CODE(S)

Code/Trivial name	Chemical name	Structural formula
M01: JAU 6476-S-methyl	2-(1-chlorocyclopropyl)-1-(2-chlorophenyl)-3-(4,5-dihydro-5-methylthio-1,2,4-triazolyl-1)-propan-2-ol	
M02: JAU 6476-sulfonic acid	1-(2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl)-1H-pyrazole-5-sulfonic acid	
M03: JAU 6476-triazolinone	1-(2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl)-1H-1,2,4-triazol-5(4H)-one	
M04: JAU 6476-desthio	2-(1-chlorocycloproyl)1-(2-chlorophenyl)-3-(1,2,4-triazol-1-yl)-propan-2-ol	

Code/Trivial name	Chemical name	Structural formula
M09: JAU 6476-benzylpropyldiol	2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)propane-1,2-diol	
M12: prothioconazole-thiazocine	6-(1-chlorocyclopropyl)-6,7-dihydro-5*H*-[1,2,4]triazolo[5,1-b][1,3]benzothiazocin-6-ol	
M18: JAU 6476-alpha-hydroxy-desthio	2-(1-chlorocyclopropyl)-1-(2-chlorophenyl)-3-(1H-1,2,4-triazol-1-yl)propane-1,2-diol	
M19: JAU 6476-acetoxy-desthio	2-(1-chlorocyclopropyl)-1-(2-chlorophenyl)-2-hydroxy-3-(1H-1,2,4-triazol-1-yl)propyl acetate