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

fluoxastrobin

finalised: 10 August 2005

SUMMARY

Fluoxastrobin 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 AG 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 of 10 January 2003 [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 fluoxastrobin, hereafter referred to as the draft assessment report (DAR), available on 2 September 2003.

The peer review was initiated on 14 October 2003 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 in an evaluation meeting on 25 May 2004. Remaining issues as well as further data made available by the notifier upon request were evaluated in a series of scientific meetings with Member State experts in September and October 2004.

A final discussion of the outcome of the consultation of experts took place with representatives from the Member States on 20 July 2005 leading to the conclusions as laid down in this report.

The conclusion was reached on the basis of the evaluation of the representative uses as fungicide as proposed by the applicant which comprises foliar spraying to control a range of fungal diseases in wheat, rye and barley at application rate up 200 g fluoxastrobin per hectare. An Annex III dossier for a representative seed treatment containing fluoxastrobin was submitted and evaluated. However, owing to issues relating to the other active substances present in the formulation used for seed treatment, it was not possible to complete overall the risk assessment.

[1] OJ No L 230, 19.8.1991, p. 1. Directive as last amended by L 70, 16.3.2005, p.1
[2] OJ No L 11, 16.01.2003, p. 52

Fluoxastrobin can be used only as fungicide. The representative formulated product for the evaluation was "HEC 5725 EC 100", an emulsifiable concentrate (EC).

Adequate methods are only available to monitor the compounds given in the respective residue definitions for food and air. Only single methods for the determination of residues are available since a multi-residue-method like the German S19 or the Dutch MM1 is not applicable due to the nature of the residues.
Sufficient analytical methods as well as methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection product are possible.

In mammals, fluoxastrobin is rapidly and nearly completely absorbed and widely distributed within the body. The highest concentrations are detected in liver, kidneys and bladder as well as in the gastrointestinal tract. No accumulation in the body is observed. The major route of excretion in rats was biliary and faecal. The metabolism is extensive and 50 metabolites are identified. The acute toxicity of fluoxastrobin is low; it is not a skin or an eye irritant, nor a skin sensitiser. There is no evidence of genotoxicity or oncogenicity. Fluoxastrobin gave no evidence of reproductive toxicity or neurotoxicity.
The acceptable daily intake (ADI) is 0.015 mg/kg bw/day, the acceptable operator exposure level (AOEL) is 0.03 mg/kg bw/day, and the acute reference dose (ARfD) is 0.3 mg/kg bw with a 100-fold assessment factor applied.
The operator risk assessment has been conducted only on the representative use in cereals as a spray application. No risk assessment for the representative use as a seed treatment in cereals is available in the DAR. The estimated operator exposure for HEC 5725 EC100 is below the AOEL without personal protective equipment (PPE) (34%), according to the German model. According to calculations with the UK POEM model, gloves have to be worn when handling the concentrate. The exposure for re-entry workers and bystanders is low (<10% of the AOEL).

Applied to wheat plants by foliar application following a seed treatment fluoxastrobin itself and its *Z*-isomer was the major residue found at harvest in straw and in grain accounting for about 86% and 80% of the total residue, respectively. Some metabolites found in plants were not observed in rat metabolism. However, due to their insignificant levels (<0.01 mg/kg) they were considered being of no concern in grain, whereas in straw some non-rat metabolites, e.g. 2-chlorophenol (M82[3]) and its glycoside (M84) are expected to be present at significant levels. However, M82 was also seen in livestock metabolism studies with fluoxastrobin, but others were not and their toxicity was not tested further. Depending on the soil, fluoxastrobin was shown to be highly persistent in soil and hence it was present in rotational crops at plant back intervals up to 328 days as the major residue. Decline of fluoxastrobin residues under processing conditions does not occur.

[3] The chemical structure of the metabolites is given in appendix 3 of the conclusion.

Fed to ruminants and poultry, fluoxastrobin was intensively metabolised resulting in a comparable pattern to that observed in rat metabolism, with the exception of some metabolites, that were not specifically found in the rat, but not considered to be of concern due to insignificant levels (<0.01 mg/kg). In a feeding study levels of relevant compounds (fluoxastrobin, its *Z*-isomer and metabolite M55) in edible animal matrices were analysed, and MRLs have been proposed.
The chronic dietary exposure assessment for consumers based on the representative GAP on cereals indicated that for all consumer subgroup the intake was less then 10% of the proposed ADI. The short term exposure of all considered consumer subgroups from individual commodities, based on consumption data of UK consumers, was all below 1% of the proposed ARfD. In an assessment of possible consumer exposure and consumer risk due to intake of metabolite M48 from drinking water the margin of safety was shown to be sufficient.

Under aerobic conditions fluoxastrobin yield the major metabolite M48-*E* and 2-chlorophenol in soil. Mineralization was generally low. Metabolite M40 was identified as a potential major anaerobic metabolite in soil. *Z*-isomer of fluoxastrobin was identified as the major soil photolysis metabolite.
As a result of the cleavage of the molecule 2-chlorophenol will be released at an expected worst case maximum amount of 49.2 % (see EFSA addendum on fate and behaviour; 26 July, 2005). The microbiologically driven degradation of 2-chlorophenol in soil was supported with a number of studies from the open scientific literature.
In field trials the *Z* isomer of fluoxastrobin was measured at up to 19 % - 22 %. The EPCO experts' meeting on fate and behaviour in the environment (EPCO 12) agreed that *Z*-isomer of fluoxastrobin should be included in the residue definition in soil and assessed for their potential ecotoxicological relevance.
Persistence of fluoxastrobin in soil may be very variable. Fluoxastrobin may behave as a moderate to high persistent compound. Metabolite M48-*E* is moderate to medium persistent in soil.
Anaerobic metabolite M40 is moderately persistent in soil under aerobic conditions.
Data available from open scientific literature show that the aerobic soil metabolite 2-chlorophenol is very low to moderately persistent in soil.
PEC soil were calculated from peak concentration after four subsequent seasons with a seed treatment and two foliar applications per season. Maximum PEC for M48 provided in the DAR is based on worst case field formation of 6.3 %. Maximum PEC soil for metabolite 2-chlorophenol is provided in the EFSA addendum on fate and behaviour.
Fluoxastrobin may be classified as low to medium mobile, M48 as medium to very high mobile and M40 high to very high mobile. The rapporteur Member State identified a Koc soil pH dependence for fluoxastrobin. No adsorption / desorption data is available for metabolite 2-chlorophenol. This has been identified as a new data requirement by EFSA.
Fluoxastrobin is stable to hydrolysis at all environmental relevant pHs. Aqueous photolysis contributes to the aqueous dissipation of fluoxastrobin. The main photolysis metabolites are: *Z* isomer of fluoxastrobin, M36 and M56.
No studies on ready biodegradability are available and fluoxastrobin was proposed to be non ready biodegradable by the experts meeting.

Only metabolite M48-*E* was seen above 10 % AR in the water phase of the water / sediment systems. Concomitant formation of metabolite 2-chlorophenol at levels above 10 % cannot be excluded. Degradation of fluoxastrobin was slow in both systems. Dissipation from the water phase was mainly due to partition in to the sediment. Mineralization was very low and bound residues increased during the study to a maximum of 12.7 % AR.
Formation of the metabolite *Z*-isomer of fluoxastrobin was observed in two irradiated aerobic water sediment studies. Contribution of photodegradation to the dissipation of fluoxastrobin from the water phase in these systems is not significant, probably due to the rapid adsorption to the sediment.
PECsw and PECsed were provided by the applicant for the representative use. Spray drift initial PECsw for the metabolite M48-*E* was calculated by the rapporteur Member State. The rapporteur Member State also provided PECsw for drainage based on their national scheme. Potential loadings to surface water through run off were not considered in the assessment presented in the DAR. Due to the fact that fluoxastrobin may be high persistent in soil, potential surface water contamination through drainage and run off may not be excluded; therefore, a comprehensive assessment taking into account spray drift, run-off, drainage and effectiveness of potential mitigation measures to reduce surface water contamination is necessary to finalize the risk assessment of the EU representative uses.
PECgw of fluoxastrobin and the metabolite M48-*E* were estimated using FOCUS-PELMO 1.1.1. Calculated concentrations of Fluoxastrobin at 1 m depth were negligible. However, metabolite M48-*E* exceeds the trigger 0.1 µg /L in eight of the nine scenarios when dependence of the adsorption Koc with the soil pH is taken into account. It is noted that for six of the scenarios the level of 0.75 µg /L is also exceeded by metabolite M48-*E*. Relevance assessment has been performed for this metabolite.
Potential groundwater contamination by soil metabolite *Z*-isomer of fluoxastrobin is not addressed in the DAR, EFSA considers that the results of the exposure assessment made for fluoxastrobin may be applied to the *Z*-isomer.
Potential groundwater contamination by soil metabolite 2-chlorophenol is not addressed in the DAR and has not been discussed during the Peer Review. EFSA identified a new data requirement since potential groundwater contamination of major soil metabolite 2-chlorophenol needs to be addressed.
Concentration of fluoxastrobin in air is expected to be negligible due to low volatility and short half life in air for reaction with OH radicals.

In the section on ecotoxicology only the risk to non-target organisms from the representative use in cereals as a spray application was assessed. No risk assessment for the representative use as a seed treatment in cereals is available in the DAR.

It should be noted that the assessment in the DAR is based on a pilot plant production. Since then the production process has been modified and optimised. Therefore, a new material accountability study and a new five batch analysis have been performed. The new resultant specification was supported by additional toxicological data, which have been peer-reviewed and accepted. An appropriate assessment with respect to ecotoxicology is still outstanding.

The risk to bees, non-target terrestrial plants and biological methods for sewage treatment is low with respect to fluoxastrobin and the metabolites for the representative use of fluoxastrobin as a spray application.

The risk to herbivorous birds and mammals can be regarded as low for the representative use of fluoxastrobin as a spray application if the risk was calculated using residue data as outlined in EPPO (1992). EFSA made a risk assessment available according to the latest guidance document on birds and mammals (SANCO/4145/2000). According to this assessment (see EFSA's addendum on ecotoxicology) the risk to mammals can be regarded as low and also the acute, short and long term risk for insectivorous and herbivorous birds as well as the acute and short term risk to granivorous birds from the representative uses evaluated can be regarded as low. But a long term risk to granivorous birds is observed (TER= 1.79 according to SANCO/4145/2000). Therefore EFSA proposes a data requirement for the notifier to submit a refinement of the long term risk to granivorous birds for the use as a seed treatment in cereals if the risk is assessed according to the latest guidance document (SANCO/4145/2000).

A high risk is identified to aquatic organisms. A bufferzone of 15 metres is needed to respect the Annex VI trigger value for the long term risk for the use of fluoxastrobin as a spray application in cereals. It was noted by the EPCO experts' meeting on ecotoxicology (EPCO 13) that additional chronic invertebrate data are available. The meeting agreed that some lowering of the chronic uncertainty would be acceptable in this case and that these additional data may be used to refine the risk assessment at MS level. Furthermore the meeting decided to address a generic question on lowering the uncertainty factor by using additional chronic species sensitivity data to EFSA's Panel on Plant Health, Plant Protection and their Residues (PPR). This generic question was forwarded to the PPR Panel by EFSA; the opinion of the Panel is still pending. The risk of the metabolite M48 to aquatic organisms is considered to be low. The experts' meeting on ecotoxicology decided that based on biological screening data, data on Daphnia and some mammalian data that it is unlikely that the *Z*-isomer is of greater toxicity than the *E*-isomer. It is noted by EFSA that also the metabolite 2-chlorophenol is considered as a major metabolite by the section on fate and behaviour. No studies with this metabolite are available and therefore EFSA proposes that a study or at least a solid argumentation regarding the effects of the metabolite 2-chlorophenol on aquatic organisms should be made available. The need for this data was not discussed at an EPCO experts meeting.

The risk to non-target arthropods was discussed at the EPCO experts' meeting. The meeting decided that based on the available data, population recovery/recolonisation in-field would be possible within one year. Therefore the meeting agreed that the risk to non-target arthropods is addressed for the representative use of fluoxastrobin as a spray application.

The risk to soil micro- and macro-organisms, including earthworms is low with respect to fluoxastrobin and the metabolites M48 and M40 for the use of fluoxastrobin as a spray application in cereals. The experts' meeting decided that it is unlikely that the *Z*-isomer is of greater toxicity than the *E*-isomer (see above). It is noted by EFSA that also the metabolite 2-chlorophenol is considered as a major metabolite by the section on Fate and behaviour. No studies with this metabolite are available and therefore EFSA proposes that a study or at least a solid argumentation regarding the

effects of the metabolite 2-chlorophenol on earthworms and soil micro-organisms should be made available. The need for this data was not discussed at an EPCO experts' meeting.

Key words: fluoxastrobin, 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 AG for inclusion of the active substance fluoxastrobin 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 of 10 January 2003.

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 fluoxastrobin, hereafter referred to as the draft assessment report (DAR), to the EPCO-Team at the Federal Office for Consumer Protection and Food Safety (BVL) in Braunschweig on 2 September 2003. This draft assessment report was distributed for consultation to the Member States and the notifier on 14 October 2003.

The comments received on the draft assessment report were evaluated and addressed by the rapporteur Member State. Based on this evaluation, representatives from Member States identified and agreed in an evaluation meeting on 25 May 2004 on data requirements to be addressed by the notifier as well as issues for further detailed discussion at expert level. A representative of the notifier was attending this meeting.

Taking into account the information received from the notifier addressing the request for further data, a scientific discussion of the identified data requirements and/or issues took place in expert meetings organised on behalf of the EFSA by the EPCO-Team in Braunschweig in September and October 2004. 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 20 July 2005 leading to the conclusions as laid down in this report.

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

In accordance with Article 8(7) of the amended Regulation (EC) No 451/2000, this conclusion summarises the results of the peer review on the active substance and the representative formulation evaluated as finalised at the end of the examination period provided for by the same Article. A list of the relevant end points for the active substance as well as the formulation is provided in appendix 1.

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

- the comments received
- the resulting reporting table (rev. 1-2 of 2 July 2004)
- the consultation report

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

- the reports of the scientific expert consultation
- the evaluation table (rev. 1-2 of 9 August 2005)

Given the importance of the draft assessment report including its addendum (compiled version of July 2005 containing all individually addenda submitted by the rapporteur Member State as well as additional addenda prepared by EFSA (birds and mammals, earthworms, route and rate of degradation is soil)) 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

Fluoxastrobin is the ISO common name for (*E*)-{2-[6-(2-chlorophenoxy)-5-fluoropyrimidin-4-yloxy]phenyl}(5,6-dihydro-1,4,2-dioxazin-3-yl)methanone *O*-methyloxime (IUPAC).

Fluoxastrobin belongs to the class of strobilurin fungicides such as azoxystrobin, kresoxim-methyl and trifloxystrobin. Fluoxastrobin is taken up via leaves and hinder the *de novo* synthesis of fatty acids by inhibition of the enzyme Acetyl-CoA carboxylase (ACCase).

The representative formulated product for the evaluation was "HEC 5725 EC 100", an emulsifiable concentrate (EC).

The evaluated representative uses as fungicide comprise foliar spraying to control a range of fungal diseasesin wheat, rye and barley at application rate up 200 g fluoxastrobin per hectare. An Annex III dossier for a representative seed treatment containing fluoxastrobin was submitted and evaluated. However, owing to issues relating to the other active substances present in the formulation used for seed treatment, it was not possible to complete overall the risk assessment.

SPECIFIC CONCLUSIONS OF THE EVALUATION

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

The minimum purity of fluoxastrobin as manufactured should not be less than 940 g/kg. At the moment no FAO specification exists.

It should be noted that the assessment in the DAR is based on a pilot plant production. Since then the production process has been modified and optimised. Therefore, a new material accountability study and a new five batch analysis have been performed. The new resultant specification was supported by additional toxicological data, which have been peer-reviewed and accepted. An appropriate assessment with respect to ecotoxicology is still outstanding.

The technical material contains no relevant impurities.

The assessment of the data package revealed no particular area of concern. The main data regarding the identity of fluoxastrobin 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 fluoxastrobin in the technical material and in the representative formulation.
Therefore, enough data are available to ensure that quality control measurements of the plant protection product are possible.

Adequate methods are only available to monitor the compounds given in the respective residue definitions for food and air, i.e. fluoxastrobin and its *Z*-isomer in food of plant and animal origin; fluoxastrobin in air.
At the moment the residue definitions for soil, groundwater and surface water are not finalised. In case 2-chlorophenol will be included, no analytical method is available to determine this compound in soil or water.
The methodology used is HPLC with MS/MS or UV-DA detection. A multi-residue method like the Dutch MM1 or the German S19 is not applicable to due the nature of the residues.

The discussion in the expert meeting on identity, physical and chemical properties and analytical methods was limited to some clarifications with respect to residue analytical methods, the composition of the formulation and the minimum purity of fluoxastrobin in the technical material.

2. Mammalian toxicology

Fluoxastrobin is intended to be used as a fungicide in cereals. The operator risk assessment has been conducted only on the representative use in cereals as a spray application. No risk assessment for the representative use as a seed treatment in cereals is available in the DAR.
In October 2004 fluoxastrobin was discussed in the EPCO experts' meeting on toxicology (EPCO 14).
The rapporteur Member State was asked to fulfil some of the open points by preparing an addendum for submission to other Member States. So far, no addendum has been produced by the rapporteur Member State. Nevertheless, information submitted by the applicant and presented by the rapporteur

Member State in the Evaluation table is considered valid to fulfil the gaps. Thus, even in the absence of the addendum, the open points can be considered fulfilled from a scientific point of view.

Toxicity tests were conducted on 4 'grades' of active substance: fluoxastrobin, for which approval is sought, HEC 5725, HEC 5725 N and HEC 5725 A[4]. The applicant stated as the manufacturing process is still in development the specification of purity and certified limits of impurities are to be regarded as preliminary only; a total of 17 impurities, plus water, are present, only one (n. 1, already considered in the former technical specification) in quantities of > 1 g/kg (see 2.2).
The issue of toxicological effects of impurities contained in the new technical specification has been discussed in the experts' meeting where a review of the toxicity data on different batches (including the final batch) and impurities summarised in the addendum 1 to the DAR was reviewed. The meeting agreed that a satisfactory investigation of the impurities had been performed and no further data were required. Thus, it can be assumed that the batches from pilot plant and large scale production plant would not differ from a toxicological point of view.

2.1 ABSORPTION, DISTRIBUTION, EXCRETION AND METABOLISM (TOXICOKINETICS)

Fluoxastrobin is rapidly and nearly completely absorbed from the gastrointestinal tract (80 - 92% of administered dose of 1 mg/kg bw within 24 - 30 hours post administration). It is widely distributed within the body of the treated animals at generally low concentrations. The highest concentrations are detected in liver, kidneys and bladder as well as in the gastrointestinal tract. No indication of significant accumulation in the body is observed. Excretion of fluoxastrobin related residues occurred fast and at a high rate. The major route of excretion in rats was biliary and correspondingly faecal (84-100% within 48 hours, mostly via bile). Fluoxastrobin is extensively metabolised (at 24-72 hours post dose the portion of unchanged parent compound is < 10% of the administered radioactivity). The metabolic pattern is complex and 50 metabolites are identified. Only a few metabolites were found to be prominent: they were hydroxylated metabolites, which still contained all 4 rings, notably M12 and M25, as well as HEC 5725-*E*-des-chlorophenyl (M48) and HEC 5725-deschlorophenyl-dioxazine-OH (M49). Metabolism in rats is qualitatively similar to that in goats and hens.

2.2 ACUTE TOXICITY

The oral toxicity of fluoxastrobin is low, i.e. LD_{50} > 2000 mg/kg bw as well as inhalation LC_{50} >5 mg/L air. The toxicity via dermal route is low (LD_{50} >2000 mg/kg bw). It is not a skin or an eye irritant. No skin sensitisation potential was observed in a study with HEC 5725 (100%*E*). However, the material tested was of much higher purity than the preliminary proposed technical specification.
The rapporteur Member State required the evaluation of the toxicological significance of impurities in fluoxastrobin in skin sensitisation. The issue was dealt with in the addendum 1 and it was concluded that only one impurity (n.1) is specified at 1% or above (cut off criteria). Therefore a skin

[4] Fluoxastrobin is the ISO proposed name and covers HEC 5725 98%*E*:2%*Z*
HEC 5725 (100% *E* isomer) covers the 100%*E* isomer.
HEC 5725 N covers the isomer ratio of 92%*E*:8%*Z*.
HEC 5725 A covers the isomer ratio of 64%E:36%Z.

sensitisation study was performed with a batch containing 3.5 % of impurities of the technical specification for which approval is sought and a negative result was obtained, showing that fluoxastrobin impurities have no sensitising potential. The experts agreed with this conclusion.

2.3 SHORT TERM TOXICITY

The short-term toxicity of fluoxastrobin has been investigated in dietary studies in rats (28-day and 90-day studies), mice (2-week and 90-day studies) and dogs (90-day and 1-year studies). A 28-day dermal toxicity study in rats has also been conducted.

The liver is the main target organ in all tested species (rats, mice and dogs). Histological changes were seen in the urinary system of rats (high doses) and dogs. Male rats were more sensitive than females to the effects of fluoxastrobin/HEC 5725 on the liver and urinary tract. Other target organs were adrenals, erythrocytes and thyroid. Reduced body weight gain was a key finding in dog studies.

In a 28-day dermal study with fluoxastrobin in rats, neither systemic nor local skin effects of toxicological importance were observed up to the highest dose level tested (1000 mg/kg bw/day).

No repeated dose inhalation were submitted, nor required.

The NOAEL in the 1-year dog study is 1.5 mg/kg bw/day (time point 12 months). The overall short term NOAEL in dogs is 3 mg/kg bw/day based on increased serum alkaline phosphatase at 8 mg in the 1-year dog study at the 90-day time point. This is also supported by effects observed at 24 mg/kg bw/day in the first 90-day dog study.

2.4 GENOTOXICITY

There is no evidence of genotoxic potential of fluoxastrobin in any of the submitted genotoxicity studies. However, most *in vitro* studies were conducted on material of higher purity than that for which approval is sought.

Hence, for additional reassurance that the impurities in fluoxastrobin are not of genotoxic concern, the applicant was asked to conduct an Ames study with a representative final full production batch.

The issue of toxicological effects of impurities has been discussed in the experts' meeting where a review of the toxicity data on different batches and impurities summarised in the addendum 1 to the DAR was reviewed. The meeting agreed that a satisfactory investigation of the impurities had been performed and no further genotoxicity data were required.

2.5 LONG TERM TOXICITY

A chronic toxicity/ carcinogenicity study in rats and a carcinogenicity study in mice with fluoxastrobin (99% *E* : 1% *Z*) were conducted.

There was no evidence of a substance-related oncogenic response in either species. A higher incidence of uterine adenocarcinoma in high dose rats compared to concurrent controls was noted; possible influences of fluoxastrobin on the female endocrine system (including mechanistic information) was discussed at the experts' meeting. The applicant provided further information (particularly for controls in the concurrent study mentioned in the DAR) to support the view that the increased incidence of uterine lesions at the top dose (adenocarcinoma and focal glandular

hyperplasia) are not substance related and hence are not of concern for hazard or risk assessment of fluoxastrobin. Notably:

1. Occurrence of these tumours was similar in high dose and study controls, and also as compared with controls in a concurrent study.
2. The incidence of focal and diffuse glandular hyperplasia at the top dose was lower than the incidence of glandular cystic hyperplasia in controls in a concurrent study (the applicant indicates that, although the terminology differs slightly, the lesions are comparable).
3. As reported in the DAR, incidence of adenocarcinoma at the top dose was lower than in controls in the concurrent study
4. There were no significant effects on reproductive performance in the multigeneration study with fluoxastrobin (indicating that fluoxastrobin does not induce endocrine effects).

In addition to glandular hyperplasia, also endometrial hyperplasia and metaplasia were seen during the study. The rapporteur Member State considered that these other hyperplastic lesions do not support the evidence of a substance related effect.

The experts' meeting agreed that the historical control data and particularly data from a study run concurrently suggested that the finding of uterine adenocarcinoma was incidental and that the concurrent control was low.

Adverse effects on the liver (reduced functional capacity, as shown by reduced plasma ALT and/or AST) were seen in both rats and mice. Increased liver weight and hepatocellular hypertrophy were also seen in mice.

There was evidence of altered calcium and phosphate homeostasis in rats, notably decreased phosphate excretion and decreased calcium content of bone. However there were no clear substance-related pathological effects on the kidney or urinary bladder of rats or mice.

Caecal enlargement and increased number of mast cells in mesenteric lymph nodes were observed in high dose rats. The increase in mast cells was considered to be a local substance-related effect and not to be indicative of an important substance-related immunological response.

The relevant NOAEL for long term toxicity and carcinogenicity is 35 mg/kg bw/day in rats.

2.6 REPRODUCTIVE TOXICITY

A 2-generation reproductive toxicity study in rats and a developmental toxicity study in rabbits were conducted with a batch of fluoxastrobin that was quantitatively similar to the preliminary proposed technical specification. The developmental toxicity study in rats was conducted with HEC 5725 (fluoxastrobin 100% *E* isomer, 98.9% purity) which was of higher purity than the preliminary proposed technical specification.

In the 2-generation study, adverse developmental effects, ie reduced body weight gain, delayed development (e.g. time to preputial separation) and reduced weight of thymus and spleen of pups were seen at the top dose. NOAEL for reproduction is 742-764 mg/kg bw/day and the parental NOAEL is 74-87 mg/kg bw/day

The applicant was asked to submit histopathological data of the thymus from multigeneration study and the evaluation of these data was presented in the addendum. The NOAEL of the study was

discussed at the experts' meeting. The NOAEL for developmental effects in the rat multigeneration study is 1000 mg/kg bw/d wasagreed on at the experts' meeting.

In the rabbit developmental toxicity study, there was evidence for a slight delay in fetal development (slight dilatation of lateral brain ventricles) at the top dose in the presence of severe maternal toxicity. There were also indications for a slight substance-related increase in the incidence of a common rib cartilage malformation and equivocal evidence for a slight increase in the incidence of one rib variation. The NOAEL for maternal toxicity in the rabbit teratogenicity study is 25 mg/kg bw/day and the developmental is 100 mg/kg bw/day. In the rat developmental toxicity study, there was no substance-related adverse maternal or developmental effect (NOAEL 1000 mg/kg bw/day).

2.7 NEUROTOXICITY

Fluoxastrobin gave a negative result with rats in an acute neurotoxicity assay which included neuropathology and a functional observation battery. There was also no evidence of substance-related neurotoxicity in a subsequent subchronic neurotoxicity assay in rats.

2.8 FURTHER STUDIES

Immunotoxicity

Studies in rats and mice did not reveal any adverse immunotoxic effects following dietary exposure for 4-13 weeks to high doses. Two studies included the plaque forming cell assay. There was however no specific investigation of the thymus, an organ for which reduced weight was observed in adults and pups in the multigeneration study.

Calcium-phosphorous homeostasis

Following further mechanistic investigations, it was concluded that exposure to fluoxastrobin resulted in reduced phosphate absorption in the intestine. A potential phosphate deficiency was counterregulated by reduced renal excretion of phosphate and renal hyper-excretion of calcium. It is proposed that increased calcium excretion in urine, together with an increase in urinary pH, led to calculi formation

Metabolites

Metabolite 48: not mutagenic in Ames test. It is a major metabolite in rats observed at levels of 10-20% of the administered dose. In six out of nine FOCUS-PELMO scenarios, the trigger of 0.75 µg/L was exceeded. No further toxicological data were provided by the applicant. Therefore, in the absence of scientific data, a refined risk assessment for consumers has been performed, based on the ADI of fluoxastrobin. The margin of safety for consumers was shown to be high, M48 intake being at a maximum *ca* 3.7% of the ADI of fluoxastrobin. (Refer to 3.3.)

The following metabolites have been identified in wheat but not in rat metabolism

M34 = HEC 5725 - ketone

M39 = HEC 5725- CA –glycol ester

M40 = HEC 5725 - carboxylic acid

M41 = HEC 5725 - OH-CA + (M42 = glycosides of M41)
M57 = HEC 5725 - OH-phenoxy-amino-PMD
M70 = HEC 5725-des-chlorophenyl-glycol-MA + (M71 = glycoside of M70)
M72 = HEC 5725-des-chlorophenyl-carboxylic acid
M82 = 2-chlorophenol + (M84 = glycoside of M82)
No genotoxicity tests, neither *in vivo* nor *in vitro* or acute toxicity test, were provided to define their toxicity. Therefore, they should be considered as toxicologically relevant and the ADI for fluoxastrobin used in the consumer risk assessment, unless new data are made available.

Impurities
Impurities 7, 15, 20, 21 and 22: rat oral LD_{50}> 2500 mg/kg bw, not mutagenic in Ames test.
Impurity 23: rat oral LD_{50} 300-500 mg/kg bw, not mutagenic in Ames test.

2.9 MEDICAL DATA

Only limited information is available. No adverse medical effects have been reported for manufacturing plant personnel.

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

ADI
The dog is the most sensitive species following exposure to fluoxastrobin. A NOAEL of 1.5 mg/kg bw/day was determined in the 1-year dog study based on reduced body weight gain and increased serum alkaline phosphatase at 8 mg/kg bw/day.
The proposed ADI is 0.015 mg/kg bw/day, with a safety factor of 100.

AOEL
The AOEL was discussed at the experts' meeting. The experts agreed on a **short-term systemic AOEL of 0.03 mg/kg bw/day** primarily based on increased serum alkaline phosphatase at 8 mg/kg bw/day in the 1-year dog study at the 90-day time point and supported by the 90-day dog study and applying a 100-fold assessment factor.

ARfD
In the most sensitive species, the dog, reduced body weight gain was seen over the first week of exposure to fluoxastrobin at high doses in 90-day and 1-year studies.
An **ARfD of 0.3 mg/kg bw** is therefore established based on applying a 100-fold assessment factor to the NOAEL of 30 mg/kg/bw/day for effects on body weight in dogs over the first week of exposure at 40 mg/kg bw/day.

2.11 DERMAL ABSORPTION

An *in vivo* dermal absorption study in monkeys has been conducted with HEC 5725 EC 100. Based on this study, a dermal absorption value for HEC 5725 (100%*E*) of 4% is considered to be appropriate for operator risk assessment of undiluted and in-use dilutions of HEC 5725 EC 100.

2.12 EXPOSURE TO OPERATORS, WORKERS AND BYSTANDERS

The representative plant protection product HEC 5725 EC100 is an EC formulation containing nominal 100 g/l fluoxastrobin for use as a fungicide on cereals.
The operator risk assessment has been conducted only on the representative use in cereals as a spray application. No risk assessment for the representative use as a seed treatment in cereals is available in the DAR.

Operator exposure

According to the intended uses submitted by the notifier the maximum applied dose is 200 g fluoxastrobin/ha and 200 to 300 litres of spray solution/ha. The proposed application method is tractor-mounted/trailed sprayer with hydraulic nozzles The estimated operator exposure for HEC 5725 EC100 is below the AOEL without PPE, according to the German model (work rate 20 ha/day). According to calculations with UK POEM, (work rate 50 ha/day) gloves have to be worn when handling the concentrate (in addition to a faceshield due to the classification of the product as an eye irritant) and when handling contaminated surfaces.

Estimated exposure presented as % of AOEL (0.03 mg/kg bw/day), according to calculations with the German and UK POEM model. The default for body weight of operator is 70 kg in the German model and 60 kg in the UK-POEM model.

Model	No PPE	With PPE*:
German	34%	-
UK POEM	207%	29%

*PPE (personal protective equipment): gloves, faceshield

Worker exposure

Worst case estimates using the German worker re-entry model together with published transfer coefficient data, indicate that the level of systemic exposure for unprotected workers entering treated cereal crops for inspection purposes is below the AOEL (8% of 0.03 mg/kg bw/day).

Bystander exposure

On the basis of generic simulated monitoring data, the level of systemic bystander exposure to fluoxastrobin resulting from the use of HEC 5725 EC100 is equivalent to 0.5% of the proposed systemic AOEL of 0.03 mg/kg bw/day.

3. Residues

3.1. NATURE AND MAGNITUDE OF RESIDUES IN PLANT

The use of Fluoxastrobin as a seed treatment followed by two foliar applications is assumed to represent the worst case scenario with respect to the consumer risk assessment. Therefore the crop metabolism and residue data has been constructed to support this pattern of use.

3.1.1. PRIMARY CROPS

The metabolism of fluoxastrobin was investigated in wheat, by applying fluoxastrobin (containing *ca* 2% *Z* isomer) radiolabelled in three positions. One application was made as a seed treatment followed by two foliar applications at a dose rate approximately twice the critical GAP.

On characterisation of the extractable radioactivity parent fluoxastrobin and its *Z* isomer was identified as the major component, accounting for up to 86% and 80% of the total radioactivity (TRR) in the grain and straw respectively. The isomer ratio in the residue at harvest was approximately 80% *E*- and 20% *Z*-isomer in grain, and 70% *E*- and 30% *Z*-isomer in straw. A range of *E*- and *Z*-isomer ratios were tested in mammalian toxicity tests. (refer to 2.) In wheat grain, forage, hay and straw several metabolites were identified or characterised. The unextractable radioactivity in the grain and straw accounted for max 6% (grain; 0.03 mg/kg) of the total radioactivity and could be attributed to breakdown products, resulting from the fragmentation of the rings and the natural incorporation of these fragments into the plant tissue. The majority of metabolites identified in the plant metabolism study were also identified in the rat metabolism studies. However, the metabolites fluoxastrobin-ketone (M34), fluoxastrobin-carboxylic acid-glycol ester (M39), fluoxastrobin-carboxylic acid (M40), fluoxastrobin-hydroxy- carboxylic acid (M41) and its glycoside (M42), fluoxastrobin-hydroxy -phenoxy-amino-pyrimidine (M57), fluoxastrobin-des-chlorophenyl-glycol-malonic acid (M70) and its glycoside (M71), fluoxastrobin-des-chlorophenyl-carboxylic acid (M72) and finally 2-chlorophenol (M82) and its glycoside (M84) were not found in the rat. From these metabolites only M82 and M84 were detected in grain but not considered to be of concern at the levels present (<0.01 mg/kg). However, in straw individual non-rat metabolites (M34, M39, M40, M42, M70, M82, M84) reached levels above 0.1 mg/kg, relating to 1N application rate. These metabolites should be considered toxicologically relevant. (refer to 2.8.) Although each of these metabolites was present at concentrations up to 0.6 mg/kg (at *ca* 2N rate) they each only contributed 0.7% or less to total radioactivity, except 2-chlorophenol (M82) and its glucoside conjugate (M84) which together were present at up to 3.3% of total radioactivity (2.6 mg/kg at *ca* 2N rate) in straw. Considering the highest residue of fluoxastrobin in straw analysed in supervised trials, levels up to 0.3 mg/kg 2-chlorophenol plus glycoside could be expected in practice. It is noted that the metabolites 2-chlorophenol (M82), M34 and M40 were, however, not found in the rat, but in livestock metabolism studies with fluoxastrobin. (refer to 3.2.)

In order to investigate effects of industrial or household processing on the nature of the residue a study simulating normal processing practice by applying representative hydrolytic conditions to a test solution was conducted. The study indicated that fluoxastrobin did not degrade during the tests.

Based on the primary plant metabolism and processing data submitted for wheat, residues in cereal crops should be defined as fluoxastrobin and *Z*-isomer for monitoring and risk assessment purposes. However, due to the fact, that the investigation of the metabolic behaviour of fluoxastrobin is limited to cereals only, a final residue definition for plants in general can not be proposed.

The magnitude of fluoxastrobin residues in grain and straw was determined in a total of 29 cereal field residue trials (13 in barley and 16 in wheat) conducted over two growing seasons in Northern and Southern European regions. In all trials, fluoxastrobin was applied as a seed treatment and developing crops received two applications as a foliar spray. All samples were analyzed with validated methods. Fluoxastrobin was the residue determined at a limit of quantification (LOQ) of 0.02 mg/kg. At harvest (> 35 days after the last application) the residues were below or at LOQ in the wheat grain samples; in barley grain the residues accounted up to 0.27 mg/kg in the Southern European trials. Fluoxastrobin residues in straw ranged between 0.1 and 6.0 mg/kg at harvest.
Studies to investigate the effects of processing on crop residues were carried out on barley and showed that residues of fluoxastrobin in the processed samples had not increased significantly with the exception of pearl barley rub off which had increased by a factor of 3.

3.1.2. SUCCEEDING AND ROTATIONAL CROPS

Fluoxastrobin turned out to be highly persistent depending on the soil. (refer to 4.1.2.) Therefore the metabolism and distribution in rotational crops was investigated in wheat, turnips and Swiss chard. The crops were grown in soil that had been treated with radio-labelled fluoxastrobin, at a rate approximately twice the critical GAP. Crops were planted 30, 157-175 and 301-328 days after application. At harvest total radioactive residues were less than 0.2 mg/kg, with the exception of wheat straw which gave residues of 1.4-2.4 mg/kg in the 30 day studies falling to 0.21-0.75 mg/kg in the 301-328 day studies.
On extraction and characterisation, one major component was identified in the crops at harvest in the 30 day studies as parent fluoxastrobin and *Z* isomer, which accounted for 14-48% of the total radioactivity in the crops, with the exception of wheat grain (<0.1%). In the crops planted 30 days after treatment, several metabolites and unknowns were noted. Individually, these were present at levels of 0.1 mg/kg or less apart from fluoxastrobin-4-hydroxyphenyl, its glucoside and glucoside malonic acid (M04, M07 and M08), which were present in wheat straw up to a level of 0.6 mg/kg. One metabolite, fluoxastrobin-des-chlorophenyl-keto-dioxazine (M54) was neither seen in primary plant metabolism nor in rat metabolism. However, levels of M54 did not exceed 0.01 mg/kg in plant parts suitable for human consumption (swiss chard) and 0.03 mg/kg in animal feed items (straw), relating to 1N application rate. The remaining unextractable radioactivity in the crops accounted for less than 0.02 mg/kg, with the exception of straw where unextractable radioactivity accounted for up to 0.28 mg/kg. The unextractable residue could be attributed to breakdown products, resulting from the fragmentation of the rings and the natural incorporation of these fragments into the plant tissue.

3.2. NATURE AND MAGNITUDE OF RESIDUES IN LIVESTOCK

The metabolism and distribution in animals was investigated in lactating goats and chickens, administering fluoxastrobin radio- labelled in two positions. The bulk of recovered radioactivity was excreted by goats (56-63%) and hens (72%). Less than 0.11% was found in the milk and less than 1.8% in the tissues of goats. Less than 0.1% was found in the eggs and less than 2.0% in the tissues of hens.

On extraction and characterisation of the milk, eggs and tissue samples, two major components were identified. These were parent fluoxastrobin and the phenoxy-hydroxypyrimidine metabolite (M55), together accounting for up to 13% of the total radioactivity in the milk; 34% in the eggs, up to 60% in meat and offal and up to 73% in the fat of goats and hens, respectively. Several other metabolites were identified and several unknowns were noted, which individually were present at levels of less than 0.4 mg/kg. Exceptions were 2-cyanophenol (M88) and 2-chlorophenol (M82), which were present in liver and kidney of goats and hens at levels up to 1.1 mg/kg. The majority of animal metabolites (edible animal products) identified in the animal metabolism study were also identified in the rat metabolism studies. However, the metabolites fluoxastrobin- hydroxy-sulfuric acid-dioxazine-OH (M24), fluoxastrobin-ketone (M34), fluoxastrobin-des-oxime-ether (M35), fluoxastrobin-di-hydroxy- sulfuric acid -amide (M43); fluoxastrobin-carboxylic acid (M40); fluoxastrobin-acetic acid (M37), fluoxastrobin-di-hydroxy-diene-carboxylic acid (M47), fluoxastrobin-di-hydroxy-diene-glycol (M44), fluoxastrobin- di-hydroxy-diene (M14); 2-chlorophenol (M82), fluoxastrobin-phenylglyoxylic acid (M90); fluoxastrobin-dioxazine-alcohol (M80), fluoxastrobin-hydroxy-mandelic acid (M92), fluoxastrobin-oxime- sulfuric acid (M33), 2-chlorophenol-sulfuric acid (M83), fluoxastrobin-hydroxy-pirimidine-OH (M64), fluoxastrobin-hydroxy-sulfuric acid-pyrimidine (M65), fluoxastrobin -di-hydroxy-pyrimidine-hydroxy-sulfuric acid (M66), fluoxastrobin-2-cyanophenol-sulfuric acid (M89), fluoxastrobin-hydroxy-sulfuric acid (M11), fluoxastrobin-ring 1,2,3-glycol (M37a), fluoxastrobin-di-hydroxy- sulfuric acid (M15a), fluoxastrobin-ring 1,2,3-des-dioxazine-nitrile (M38a) and fluoxastrobin-tri-hydroxy- sulfuric acid (M25a) were not found in the rat, but were not considered to be of concern at the levels present in the studies. As the studies were carried out at highly exaggerated doses compared to the expected exposure, it is unlikely that any of the compounds despite fluoxastrobin and metabolite M55 would be present at levels greater than 0.01 mg/kg, in N rate studies.

Therefore, for risk assessment purposes, the residue definition for animal products should be the sum of fluoxastrobin, its *Z*-isomer plus the metabolite phenoxy-hydroxypyrimidine (M55) expressed as fluoxastrobin. For monitoring the residue definition fluoxastrobin and *Z*-isomer is proposed.

Fluoxastrobin and *Z*-isomer in a ratio of 65% *E*-isomer, 35% *Z*-isomer was fed to dairy cows in a feeding study in order to reflect the isomer ratio occurring in potential feed items. (refer to 3.1.) Fluoxastrobin, the *Z*-isomer and metabolite M55 was analysed, and positive results were found in milk and tissue samples. Based on calculated intakes and the ruminant metabolism and transfer studies MRLs for animal products, except for poultry products have been proposed. For poultry products MRLs were not proposed due to the predicted intake being less than 0.1 mg/kg diet.

3.3. CONSUMER RISK ASSESSMENT

The total intake for an adult based on the WHO model (GEMS/Food European diet) was less than 3% of the proposed ADI. National Estimates of Daily Intake (NEDI) were calculated for UK consumers with the UK Rees/Day model (Two highest 97.5th percentile intakes plus mean intakes from other food). Total intakes for all considered consumer groups were all significantly below the ADI of 0.015 mg/kg bw/day, accounting for less than 10% of the proposed ADI.

Since the level of 0.75 µg /L is exceeded by metabolite M48 in groundwater (refer to 4.2.2) and the full package of toxicological data for M48 has not been submitted, a consumer risk assessment needs to be performed. (refer to 2.8.) The rapporteur Member State proposed a maximum allowable concentration (MAC) in drinking water, based on assumptions for adult consumers, which was not exceeded by the predicted level of 3.65 µg /L. However, the fluid intake per kg of body weight is much higher for children than for adults Therefore EFSA made the following assessment for infants and children, based on the default assumptions laid down in the WHO Guidelines of drinking water quality. For a child of 10 kg consuming 1L/ day and an infant consuming 0.75 L/day the estimated daily intakes of metabolite M48 are 0.00037 mg/kg bw and 0.00055 mg/kg bw, respectively, accounting for *ca* 2.5% and 3.7% of the ADI of fluoxastrobin. With regard to the limited data on the toxicity of M48, the margin of safety is considered sufficient to conclude that the predicted level of M48 in groundwater is unlikely to pose a dietary risk to consumers.

National Estimates of Short term dietary intakes (NESTI) for fluoxastrobin have been estimated using UK food consumption data. Intakes for individual commodities were all significantly below the proposed ARfD of 0.3 mg/kg bw/day, accounting for less than 1% of the proposed ARfD. An acute risk due to the intake of metabolite M48 from drinking water is not expected.

3.4. PROPOSED MRLS

On the basis of the residues data submitted, the following MRLs are proposed:

Wheat, Rye	0.05
Barley	0.5
Milk	0.01
Meat (ex poultry)	0.02
Fat, Liver (ex poultry)	0.05
Kidney	0.1

CAC MRLs have not yet been proposed or established for fluoxastrobin.

4. Environmental fate and behaviour

Fluoxastrobin was discussed in experts' meeting on Fate and Behaviour in the Environment EPCO 12 (September 2004). For some of the sections in fate and behaviour, the assessment is based on the additive loadings arising from the two representative uses presented by the Notifier in document D:

seed treatment followed by spray application. Assessment of the seed treatment uses has not been completed for some DAR sections (physical and chemical properties, toxicology and ecotoxicology) and therefore labelled grey in the table of representative uses. The inclusion of the seed treatment loadings in the assessment of some of the environmental compartments may results in a slightly worst case with respect to the assessment that would result if only spray drift loadings were considered.

4.1. FATE AND BEHAVIOUR IN SOIL

4.1.1. ROUTE OF DEGRADATION IN SOIL

Fluoxastrobin metabolism in soil under dark aerobic conditions at 20 °C was investigated in two studies with four different soils using the compound labelled at the methoxyiminotolyl ring. Two of the soils were additionally tested with fluoxastrobin labelled at the pyrimidine ring. The four soils covered a range of pH (6.1 – 8.1), organic matter content (0.43 % - 4.51 %) and soil textures.

Under aerobic conditions cleavage of the chlorophenyl moiety of fluoxastrobin yield the major metabolite **M48-*E*** (HEC 5725-des-chlorophenyl, maximum 30.2 % AR after 30 d) and **2-chlorophenol** (see below). No significant formation of the *Z* isomer of fluoxastrobin is observed under dark conditions. Other minor metabolites were formed by hydroxylation of the chlorophenyl moiety or cleavage of the dioxazin ring. Mineralization was generally low in the experiments performed with the compound labelled at the methoxyiminotolyl ring (CO_2: 1.0 % AR – 12.5 AR after 120 d) but slightly higher in one of the experiments performed with fluoxastrobin labelled at the pyrimidine ring (CO_2: 4 % AR- 37.3 % AR after 120 d). Unextractable residues reached a maximum of 71 % AR after 120 d in one of the soils but were below 70 % in the rest of experiments (13. 4 % AR – 58 % AR after 120 d).

No study to investigate the anaerobic degradation in soil of fluoxastrobin is available. However, in an anaerobic water sediment study (sediment: pH 5.3, organic carbon 0.46 %, clay 37.3 %) major metabolite **M40** (HEC 5725 carboxylic acid, max 21.1 % after 360 d) is formed. This metabolite was identified as a potential major anaerobic metabolite in soil by the rapporteur Member State. While for the representative uses proposed extended periods of anaerobic conditions are not expected, further data may need to be required by MS to consider uses that could result in extended anaerobic periods.

A soil photolysis study at 20 °C in one soil irradiated with a xenon lamp for 15 d is available. ***Z*-isomer of fluoxastrobin** (maximum 22.2 %) was identified as the major soil photolysis metabolite.

Any of the laboratory soil studies uses fluoxastrobin labelled at the chlorophenyl ring. As a result of the cleavage of the molecule this ring will be released as 2-chlorophenol (expected maximum amount equivalent to 49.2 % molar ratio with respect to the parent fluoxastrobin, as calculated by EFSA based on worst case assumptions, see EFSA addendum 26, July, 2005). The microbiologically driven degradation of 2-chlorophenol in soil was supported with a number of studies from the open scientific literature.

Eight field dissipation trials in typical agricultural regions of the northern and southern Europe are available. Four of the trials were performed on bare soil and the other four cropped first and second year with spring barley and grass respectively. In bare soil field trials the *Z* isomer of fluoxastrobin was measured at up to 22 %. In plots were crop emerged post treatment a slightly lower level of 19 % was attained for this metabolite.

EPCO experts' meeting on fate and behaviour in the environment (EPCO 12, September 2004) agreed that *Z*-isomer of fluoxastrobin should be included in the residue definition in soil and assessed for their potential ecotoxycological relevance.

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

Rate of degradation of fluoxastrobin in soil was investigated in the same studies used to establish the route of degradation. Persistence of fluoxastrobin in soil may be very variable. Depending on the soil, fluoxastrobin may behave as a moderate to high persistent compound ($DT_{50\ lab\ 20\ °C}$ = 12 d to 356 d). Also a high variability on the rate of degradation was observed in field studies ($DT_{50\ field}$ = 16 d – 119 d).

Rate of aerobic degradation of metabolite M48 in soil was calculated from the studies performed with the parent compound with a multi-compartmental model assuming first order degradation in all the degradation steps. Three reliable values were obtained for the half life indicating that this metabolite is moderate to medium persistent in soil ($DT_{50\ lab\ 20\ °C}$ = 34 d – 100 d).

Aerobic degradation in soil at 20 °C of anaerobic metabolite M40 was investigated in soil in a separated study with unlabelled material in three different soils covering a range of pH (7.2 – 7.6), organic carbon content (0.83 % - 2.11 %) and soil textures. According the results of this study anaerobic metabolite M40 is moderately persistent in soil under aerobic conditions ($DT_{50\ lab\ 20\ °C}$ = 11 d – 25 d).

Data available from open scientific literature show that the aerobic soil metabolite 2-chlorophenol is very low to moderately persistent in soil (DT_{50} = 0.6 d – 23 d, see EFSA addendum 26, July, 2005).

PEC soil were calculated from peak concentration after four subsequent seasons with a seed treatment and two foliar applications per season using the worst case field half life (DT_{50} = 119 d) for the parent compound. Maximum PEC for M48 provided in the DAR is based on worst case field formation of 6.3 %. Maximum PEC soil for 2-chlorophenol has been calculated by EFSA based on worst case formation estimate of 49.18 % (see EFSA addendum 26, July, 2005).

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

Batch equilibrium adsorption / desorption studies are available for fluoxastrobin, M48 and M40 with four different soils. According these studies fluoxastrobin may be classified as low to medium mobile (Koc = 424 – 1582 mL / g), M48 (actual isomer tested not specified in the DAR) as medium to very high mobile (Koc = 14 – 181 mL / g) and M40 high to very high mobile (Koc = 37 – 87 mL / g). rapporteur Member State identified a adsorption pH dependence, with a reduced adsorption with increasing soil pH. No adsorption / desorption data is available for metabolite 2-chlorophenol. This is necessary to address the potential groundwater contamination by this metabolite and has been identified as a new data requirement by EFSA.

No column leaching, field leaching or lysimeter studies are provided in the dossier of fluoxastrobin.

4.2. FATE AND BEHAVIOUR IN WATER

4.2.1. SURFACE WATER AND SEDIMENT

The hydrolytic stability of fluoxastrobin was studied in sterile aqueous buffer solutions (pH 4, 7 and 9). Fluoxastrobin is stable at all environmental relevant pHs. Aqueous photolysis of fluoxastrobin was studied in sterile aqueous buffer at pH 7 with fluoxastrobin labelled at the methoxyiminotolyl ring and with fluoxastrobin labelled at the chlorophenyl ring. Photolysis contributes to the aqueous dissipation of fluoxastrobin. Calculations using GC-SOLAR and Frank and Klöpffer predicted an environmental half-life for fluoxastrobin in the range of 2.3 d – 20 d. The main photolysis metabolites are: *Z* isomer of fluoxastrobin (max 11.2 % AR after 1 d), **M36** (HEC 5725-oxazepine, max 23.6 % AR after 8d, end of the study) and **M56** (HEC 5752-phenoxy-aminopyrimidine, max 4.7 % AR after 8d, end of the study).

No studies on ready biodegradability of fluoxastrobin are available. Fluoxastrobin was proposed to be non ready biodegradable by the experts meeting (EPCO 12).

Two aerobic water sediment systems at 20 °C under dark conditions were investigated using fluoxastrobin labelled at the methoxyiminotolyl ring. Among the four identified metabolites only M48-*E* was seen above 10 % AR in the water phase (max 15.9 % AR after 122 d, end of the study). Concomitant formation of 2-chlorophenol should be assumed and the formation of this metabolite at levels above 10 % of the applied quantity cannot be excluded. Degradation of fluoxastrobin was slow in both systems ($DT_{50\ whole\ system}$ = 144 d – 188 d). Dissipation from the water phase was mainly due to partition in to the sediment ($DT_{50\ water}$ = 25.6 d – 42.1 d, calculated by ACSL Optimiza Software package 1996 with a multi-compartmental model assuming negligible degradation into the sediment phase). Mineralization was very low (CO_2: max 2.9 % AR after 122 d, end of the study). Bound residues increased during the study to a maximum of 12.7 % AR.

Additionally, a study with two irradiated (Suntest® with Xenon lamp) aerobic water sediment at 25 °C systems is available. The study lasted for 288 h (12 d) and sediments were only analyzed at the end of the study. Formation of the metabolite *Z*-isomer of fluoxastrobin was observed (max in water: 11.9 % AR after 24 h; sediment: 13.1 % AR after 288 h). The other major photolysis metabolite M36 was not found during this study. Photolysis metabolite M56 was not analyzed. Contribution of photodegradation to the dissipation of fluoxastrobin from the water phase in these systems is not significant, probably due to the rapid adsorption to the sediment.

PECsw were provided by the applicant assuming spray drift from two 200 g/ha applications with 14 days interval taking as basis the worst case dissipation DT_{50} observed in dark water sediment study. Whereas the methodology employed in the calculation deviates of the standard simple drift calculations, the deviations result in a worst case and were accepted by the rapporteur Member State. Spray drift initial PECsw for the metabolite M48-*E* was calculated by the rapporteur Member State based on the maximum amount of this metabolite observed in the water sediment systems.

The rapporteur Member State also provided PECsw for drainage based on their national scheme,[5] for the UK risk assessment. The worst case drainflow PECsw for parent fluoxastrobin and the metabolite

[5] PSD Data requirements handbook, Chapter 6.5, pp 32-35. PSD, Mallard House, Kings Pool, 3 Peasholme Green, York, YO107OX.

M48-*E* under this scheme are higher than the ones resulting from spray drift only, indicating potential contribution of drainage to surface water contamination. Higher tier modelling was performed by the rapporteur Member State with MACRO and using a drainage ditch scenario for the UK assessment.
Potential loadings to surface water through run off were not considered in the assessment presented in the DAR. Due to the fact that fluoxatrobin may be high persistent in soil, potential surface water contamination through drainage and run off may not be excluded; therefore, a comprehensive assessment taking into account spray drift, run-off, drainage and effectiveness of potential mitigation measures to reduce surface water contamination is necessary to finalize the risk assessment of the EU representative uses.
Worst case maximum PECsed were calculated by the rapporteur Member State based on spray drift and maximum amount of fluoxastrobin observed in the sediment of the aerobic water sediment systems. Pseudo PECsw for use in the sediment dweller organism risk assessment was calculated in the same way. Neither drainage nor run off were considered for the PECsed calculation.

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

PECgw of Fluoxastrobin and the aerobic metabolite M48-*E* were estimated using FOCUS-PELMO 1.1.1. for the nine EU scenarios and the representative uses, using input parameters selected according FOCUS guidelines. Calculated concentrations of Fluoxastrobin at 1 m depth were negligible. However, for metabolite M48-*E* exceeds the trigger 0.1 µg /L in seven of the nine scenarios when the mean Koc was used. The rapporteur Member State recalculated some of the scenarios to take into account the observed dependence of the adsorption Koc with the soil pH. Then, only Piacenza scenario show concentrations of metabolite M48-*E* below 0.1 µg /L. It is noted that for six of the scenarios the level of 0.75 µg /L is also exceeded by metabolite M48-*E*. Results of the relevance assessment for M48-*E* are summarized in the table found in the section 6 for residue definitions.
Potential groundwater contamination by soil metabolite *Z*-isomer of fluoxastrobin is not addressed in the DAR and has not been discussed during the Peer Review. Since physical and chemical properties and behaviour in the environment of this metabolite is expected to be very similar to the parent, EFSA considers that the results of the exposure assessment made for fluoxastrobin may be applied to the *Z*-isomer.
Potential groundwater contamination by soil metabolite 2-chlorophenol is not addressed in the DAR and has not been discussed during the Peer Review. EFSA identified a new data requirement since potential groundwater contamination of major soil metabolite 2-chlorophenol needs to be addressed.

4.3. FATE AND BEHAVIOUR IN AIR

Concentration of fluoxastrobin in air is expected to be negligible due to low volatility and short half life in air for reaction with OH radicals.

http://www.pesticides.gov.uk/psd_pdfs/registration_guides/data_reqs_handbook/datareqhandbook.pdf

5. Ecotoxicology

In the section on ecotoxicology only the risk to non-target organisms from the representative use in cereals as a spray application was assessed. No risk assessment for the representative use as a seed treatment in cereals is available in the DAR.

It should be noted that the assessment in the DAR is based on a pilot plant production. Since then the production process has been modified and optimised. Therefore, a new material accountability study and a new five batch analysis have been performed. The new resultant specification was supported by additional toxicological data, which have been peer-reviewed and accepted. An appropriate assessment with respect to ecotoxicology is still outstanding.

Fluoxastrobin was discussed in the experts' meeting on ecotoxicology (EPCO 13) in September 2004.

5.1. RISK TO TERRESTRIAL VERTEBRATES

The risk to birds and mammals was calculated using residue data as outlined in EPPO (1992).
The risk was calculated for an herbivorous and insectivorous bird as the representative use is in cereals at a stage where also the crop itself is likely to be grazed. The acute, short and long term toxicity to birds can be regarded as low in the first tier risk assessment (TER > 186, >112 and = 10.3 respectively) for the representative use of fluoxastrobin as a spray application.

Furthermore the risk to herbivorous and insectivorous mammals was calculated. The TER values for the acute and long term risk (>62 and >5141 respectively) are above the Annex VI trigger values indicating a low acute and long term risk to mammals for the representative use of fluoxastrobin as a spray application.

As the risk to birds and mammals was calculated according to EPPO (1992), a similar risk assessment was made available by EFSA based on the "Guidance Document on Risk Assessment for Birds and Mammals under Council Directive 91/414/EEC" (Sanco/4145/2000 of 25 September 2002). In addition to the scenarios for an herbivorous and insectivorous bird and mammal also the risk for a granivorous bird and mammal was assessed as one of the representative uses is as a seed treatment in cereals. According to this assessment (see addendum by EFSA) the risk to mammals can be regarded as low as the calculated acute and long term TER values (TER-values are ≥ 42.22 and ≥ 43.01 respectively) are above the respective Annex VI trigger values for the representative uses evaluated. Also the acute, short and long term risk for insectivorous and herbivorous birds as well as the acute and short term risk to granivorous birds from the representative uses evaluated (TER-values are ≥ 70.18, ≥ 33.89 and ≥ 8.45 for the acute, short and long term risk respectively) can be regarded as low as the appropriate Annex VI trigger values were not breached. The Annex VI trigger value for the long term risk to granivorous birds is breached (TER = 1.79) indicating a high long term risk to granivorous birds in the first tier risk assessment. Therefore EFSA proposes a data requirement for

the notifier to submit a refinement of the long term risk to granivorous birds for the representative use as a seed treatment if the risk is calculated according to the latest guidance document (SANCO/4145/2000).

As the logPow is below 3 the risk from secondary poisoning to birds and mammals is considered to be low.

5.2. RISK TO AQUATIC ORGANISMS

Americamysis bahia was the most sensitive species from all aquatic species tested with fluoxastrobin both on an acute and on a long term time scale. *Oncorhynchus mykiss*, *Daphnia magna* and *Pseudokircherniella subcapitata* were tested with the lead formulation HEC 5725 EC 100. *Oncorhynchus mykiss* was the most sensitive organism to this lead formulation. The lead formulation is of similar toxicity to the tested aquatic organisms than the active substance.
The choice of endpoint for the risk assessment was discussed during the EPCO experts' meeting. The meeting considered that data for the mysid shrimp, which is a salt water species, should be used for both the acute and chronic risk assessments.
PECsw was calculated assuming spray drift from two 200 g/ha applications with 14 days interval (see point 4.2).
Based on the endpoint for mysid shrimp the acute TER is 28. The EPCO experts' meeting agreed that the acute risk to aquatic organisms is low, without the need for risk mitigation measures, based on the number of species tested.
Furthermore the EPCO experts' meeting agreed that the long term risk to aquatic organisms could be regarded as low if a bufferzone of 15 metres is taken into account. Also this long term TER value is based on data from a mysid shrimp study. However it was noted by the meeting that additional chronic invertebrate data are available. The meeting agreed that some lowering of the chronic uncertainty would be acceptable in this case and that these additional data may be used to refine the risk assessment at MS level. Furthermore the meeting decided to send a generic question on lowering the uncertainty factor by using additional chronic species sensitivity data to the PPR Panel. This generic question was forwarded to the PPR Panel by EFSA. The opinion of the Panel is still awaited.

As in the water sediment study the content of active substance was above 10% of the AR at or after 14 days, studies with the active substance on sediment dwelling organisms are considered necessary. A study with the active substance on *Chironomus riparius* is available indicating a low risk to sediment dwelling organisms without the need for risk mitigation measures.

Furthermore the metabolites HEC 5725-deschlorophenyl and HEC 5725-carboxylic acid were tested on *Oncorhynchus mykiss*, *Daphnia magna* and *Pseudokircherniella subcapitata*. HEC 5725-carboxylic acid was additionally tested on *Chironomus riparius.* The metabolites are both more than one order of magnitude less toxic to aquatic organisms than the parent compound. The risk to aquatic organisms from both these metabolites is considered to be low. The EPCO experts' meeting discussed the relevance of the *Z*-isomer of fluoxastrobin. The meeting decided that based on biological

screening data, data on Daphnia and some mammalian data that it is unlikely that the *Z*-isomer is of greater toxicity than the *E*-isomer. It is noted by EFSA that also the metabolite 2-chlorophenol is considered as a major metabolite by the section on Fate and behaviour. No studies with this metabolite are available and therefore EFSA proposes that a study or at least a solid argumentation regarding the effects of the metabolite 2-chlorophenol on aquatic organisms should be made available. The need for this data was not discussed at an EPCO experts' meeting.

Fluoxastrobin is not an herbicide so studies on aquatic plants are not considered necessary.

Although the Log Pow is below 3, a study on bioconcentration in fish is made available. The resulting BCF is below the Annex VI trigger value of 100 for not readily biodegradable compounds indicating a low risk for bioconcentration in fish.

5.3. RISK TO BEES

Acute contact and oral toxicity studies, both with fluoxastrobin and the lead formulation HEC 5725 EC 100, are available. The resulting HQ values do not breach the appropriate Annex VI trigger value indicating a low risk to bees for the representative use of fluoxastrobin as a spray application.

5.4. RISK TO OTHER ARTHROPOD SPECIES

Standard and/or extended laboratory studies with Aphidius rhopalosiphi, Typhlodromus pyri, Aleochara bilineata, Poecilus cupreus, Coccinella septempunctata and Chrysoperla carnea are available. Furthermore a semi-field trial with A. rhopalosiphi and a residue decline study is available.
A risk assessment according to Escort I and to Escort II are available in the DAR. Effects above 30% (the Annex VI trigger value) were observed during the standard and extended laboratory study with A. rhopalosiphi (82% mortality at 200 g a.s./ha in the extended laboratory study) and C. septempunctata (75% mortality at 200 g a.s./ha in the extended laboratory study) and the laboratory study with C. carnea (82% mortality at 200 g a.s./ha). A semi-field trial with A. rhopalosiphi is available. In this study a reduction of 32% of the reproductive capacity was observed when the adults were exposed to fresh residues when fluoxastrobin was applied twice with an interval of 14 days at 200 g a.s./ha. A reduction of 13% was observed when adults were exposed to aged deposits (14DAT2). This indication of a lack of persistent effect is supported by the results of the residue decline study in which more than 80% loss of active substance in treated foliage was seen after 7 days. An off-field risk assessment according to Escort II is available in the DAR. Both the HQ-values for the standard indicator species A. rhopalosiphi and T. pyri (HQ= 0.089 and 0.05 respectively) are below 2, indicating a low risk to non-target arthropods off-field.
The risk to non-target arthropods was discussed at the EPCO experts' meeting. The meeting decided that based on the available data, population recovery/recolonisation in-field would be possible within one year. Therefore the meeting agreed that the risk to non-target arthropods is addressed for the representative use of fluoxastrobin as a spray application.

5.5. RISK TO EARTHWORMS

The Predicted Environmental Concentration (PEC) in soil was calculated in the section on Fate and behaviour for the combined use of the seed treatment and spray application in cereals.
Studies on the acute toxicity to earthworms from fluoxastrobin and the metabolites HEC 5725-deschlorophenyl and HEC 5725-carboxylic acid are available. The endpoint for fluoxastrobin was corrected for the organic content of the test soil as the LogPow exceeds 2. The logPow of the metabolites is < 2 and therefore no correction factor is required for the metabolites. The corresponding TER-values do not breach the Annex VI trigger value, indicating a low acute risk to earthworms for the use of fluoxastrobin as a spray application in cereals.

Studies on the long term toxicity to earthworms from the EC lead formulation and the metabolite HEC 5725-deschlorophenyl are available. The corresponding TER-values do not breach the Annex VI trigger value, indicating a low long term risk to earthworms for the use of fluoxastrobin as a spray application in cereals.

It was noted by EFSA that the rapporteur Member State revised the PECsoil values for the metabolite M48 after the EPCO experts' meeting and hence also the corresponding TER values for earthworms and soil macro-organisms in the List of endpoints. EFSA agrees with the revised PECsoil calculations for the metabolite M48. For reasons of transparency the calculation leading to these revised TER values are given by EFSA in an addendum. The risk to earthworms from this metabolite can be considered as low.

The EPCO experts' meeting discussed the relevance of the *Z*-isomer of fluoxastrobin. The meeting decided that based on biological screening data, data on Daphnia and some mammalian data that it is unlikely that the *Z*-isomer is of greater toxicity than the *E*-isomer. It is noted by EFSA that also the metabolite 2-chlorophenol is considered as a major metabolite by the section on Fate and behaviour. No studies with this metabolite are available and therefore EFSA proposes that a study or at least a solid argumentation regarding the effects of the metabolite 2-chlorophenol on earthworms should be made available. The need for this data was not discussed at an EPCO experts' meeting.

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

Studies on the effects of fluoxastrobin and the metabolite HEC 5725-deschlorophenyl on collembolan are available. The lead formulation HEC 5725 was tested on the predacious soil mite *Hypoaspis aculeifer* and furthermore a soil litter bag study is available.
The calculated TER-values for collembola and *H. aculeifer* are above 5, the trigger value mentioned in the Guidance Document on Terrestrial Ecotoxicology (SANCO/10329/2002).
It was noted by EFSA that the rapporteur Member State revised the PECsoil values for the metabolite M48 after the EPCO experts' meeting and hence also the corresponding TER values for earthworms and soil macro-organisms in the List of endpoints. EFSA agrees with the revised PECsoil calculations for the metabolite M48. For reasons of transparency the calculation leading to these revised TER

values are given by EFSA in an addendum. The risk to *Folsomia candida* from this metabolite can be considered as low.
Soil concentrations were analytically verified during the litterbag study and only 50% of the initial PEC was achieved although the test product was applied according to the GAP. No inhibition of litter degradation was observed during this study.
Based on this litterbag study and based on the low risk to earthworms, collembola and soil mites, it was concluded that the risk to soil macro-organisms and soil organic matter decomposition processes from the use of fluoxastrobin as a spray application in cereals is low.

5.7. RISK TO SOIL NON-TARGET MICRO-ORGANISMS

The effects of fluoxastrobin and the metabolites HEC 5725-deschlorophenyl and HEC 5725-carboxylic acid were tested on soil microbial respiration and nitrogen transformation (only effects on nitrogen transformation were assessed for HEC 5725-carboxylic acid). No deviations of more than 25 % after 28 days were observed (i.e. no breaching of the Annex VI trigger value) at a dose rate exceeding the initial PEC and hence the risk to soil non-target micro-organisms from fluoxastrobin and the metabolites HEC 5725-deschlorophenyl and HEC 5725-carboxylic acid is considered to be low for the use of fluoxastrobin as a spray application in cereals.

The EPCO experts' meeting discussed the relevance of the *Z*-isomer of fluoxastrobin. The meeting decided that based on biological screening data, data on Daphnia and some mammalian data that it is unlikely that the *Z*-isomer is of greater toxicity than the *E*-isomer. It is noted by EFSA that also the metabolite 2-chlorophenol is considered as a major metabolite by the section on Fate and behaviour. No studies with this metabolite are available and therefore EFSA proposes that a study or at least a solid argumentation regarding the effects of the metabolite 2-chlorophenol on soil micro-organisms should be made available. The need for this data was not discussed at an EPCO experts' meeting.

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

Screening studies on the effects of fluoxastrobin on non-target terrestrial plants are available. Effects were less than 20% at a dose rate exceeding the highest representative use rate. Therefore the risk to non-target plants is considered to be low for the use of fluoxastrobin as a spray application in cereals.

5.9. RISK TO BIOLOGICAL METHODS OF SEWAGE TREATMENT

The respiration rate EC_{50} for fluoxastrobin exceeds 10000 mg a.s./L. Based on this study the risk to biological methods of sewage treatment is considered to be low for the use of fluoxastrobin as a spray application in cereals.

6. Residue definitions

Soil

Definitions for risk assessment: fluoxastrobin, *Z*-isomer of fluoxastrobin, M48-*E*, 2-chlorophenol, M40 (anaerobic metabolite).

Definitions for monitoring: fluoxastrobin, *Z*-isomer of fluoxastrobin, 2-chlorophenol (assessment needs to be finalized).

Water

Groundwater

Definitions for risk assessment: fluoxastrobin, *Z*-isomer of fluoxastrobin, M48-*E*, 2-chlorophenol,

Definitions for monitoring: fluoxastrobin, 2-chlorophenol (assessment needs to be finalized).

Surface water

Definitions for risk assessment: fluoxastrobin, *Z*-isomer of fluoxastrobin, M48-*E*, 2-chlorophenol, M-40 (anaerobic metabolite).

Definitions for monitoring: fluoxastrobin, *Z*-isomer of fluoxastrobin, 2-chlorophenol (assessment needs to be finalized).

Air

Definitions for risk assessment: fluoxastrobin

Definitions for monitoring: fluoxastrobin

Food of plant origin

Definitions for risk assessment: fluoxastrobin and *Z*-isomer of fluoxastrobin

Definitions for monitoring: fluoxastrobin and *Z*-isomer of fluoxastrobin

Food of animal origin

Definitions for risk assessment: fluoxastrobin and *Z*-isomer of fluoxastrobin, plus the metabolite phenoxy-hydroxypyrimidine (M55) expressed as fluoxastrobin

Definitions for monitoring: fluoxastrobin and *Z*-isomer of fluoxastrobin

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

Soil

Compound (name and/or code)	Persistence	Ecotoxicology
fluoxastrobin	Moderate to high persistent $DT_{50\ field}$ = 16 d – 119 d	See 5.5, 5.6 and 5.7
M48-*E*	Moderate to medium persistent $DT_{50\ lab\ 20\ °C}$ = 34 d – 100 d	The risk to earthworms, *Folsomia candida* and soil micro-organisms can be regarded as low.
2-chlorophenol	Very low to moderately persistent DT_{50} = 0.6 d – 23 d (from open scientific open literature)	No data available.
M40 (anaerobic metabolite)	Moderately persistent (under aerobic conditions) $DT_{50\ lab\ 20\ °C}$ = 11 d – 25 d	The risk to earthworms and soil micro-organisms can be regarded as low.
Z-isomer of fluoxastrobin (photolysis metabolite)	No direct experimental data available. Persistence expected to be in the range of the parent fluoxastrobin. Moderate to high persistent $DT_{50\ field}$ = 16 d – 119 d	The EPCO experts' meeting decided that based on biological screening data, data on Daphnia and some mammalian data that it is unlikely that the *Z*-isomer is of greater toxicity than the *E*-isomer.

Groundwater

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
Fluoxastrobin	low to medium mobile Koc = 424 – 1582 mL / g	FOCUS-PELMO: No, 0.1 µg /L trigger not exceeded.	Yes	Yes	See 5.2
M48-*E*	medium to very high mobile Koc = 14 – 181 mL / g	FOCUS-PELMO 1.1.1.: Yes, 0.1 µg /L trigger exceeded. 0.75 µg /L exceeded by six of nine scenarios.	No pesticidal activity	No acute toxicity data available. Not mutagenic. Not relevant according to consumer risk assessment (max 3.7% of the ADI of fluoxastrobin)	M48 is one order of magnitude less toxic to aquatic organisms than the parent compound.
2-chlorophenol	**Not assessed, needs to be assessed**	**Not assessed, needs to be assessed**	No data available.	No data available	No data available.
Z-isomer of fluoxastrobin (photolysis metabolite)	**Not assessed, Expected to have analogous behaviour than the parent fluoxastrobin**	Not assessed, no assessment required.	Less fungicidal activity than the *E*-isomer. No herbicidal and insecticidal activity.	No data available	The EPCO experts' meeting decided that based on biological screening data, data on Daphnia and some mammalian data that it is unlikely that the *Z*-isomer is of greater toxicity than the *E*-isomer.

Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Fluoxastrobin (water and sediment)	See 5.2
M48-*E* (only water)	The risk to aquatic organisms is considered low based on an acute toxicity study with fish, an acute toxicity study with *Daphnia magna* and a toxicity study with algae. M48 is one order of magnitude less toxic to aquatic organisms than the parent compound.
Z-isomer of fluoxastrobin (water and sediment)	The EPCO experts' meeting decided that based on biological screening data, data on Daphnia and some mammalian data that it is unlikely that the *Z*-isomer is of greater toxicity than the *E*-isomer.
2-chlorophenol	No data available.
M-40 (anerobic metabolite; water and sediment)	The risk to aquatic organisms is considered low based on an acute toxicity study with fish, an acute toxicity study with *Daphnia magna*, a toxicity study with algae and a study with *Chironomus riparius*. M40 is one order of magnitude less toxic to aquatic organisms than the parent compound.

Air

Compound (name and/or code)	Toxicology
Fluoxastrobin	Not toxic via inhalation during single exposure (LC_{50}> (mg/L). No data available for repeated exposures.

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

- Depending on the final decision to include 2-chlorophenol in the residue definitions for soil and water (ground and surface), an analytical method for enforcement purposes could be necessary (refer to chapter 6)
- Adsorption / desorption study or data on soil metabolite 2-chlorophenol (identified by EFSA in the course of preparation of the conclusion; relevant for all representative uses evaluated; no submission date yet proposed by the notifier, refer to point 4.1.3).
- Due to the fact that fluoxastrobin may be highly persistent in soil, potential surface water contamination through drainage and run off may not be excluded; therefore, a comprehensive assessment taking into account spray drift, run-off, drainage and effectiveness of potential mitigation measures to reduce surface water contamination is necessary to finalize the risk assessment of the EU representative uses (relevant for all representative uses evaluated; no submission date yet proposed by the notifier, refer to point 4.2.1).
- Potential groundwater contamination by soil metabolite 2-chlorophenol needs to be addressed (identified by EFSA in the course of preparation of the conclusion; relevant for all representative uses evaluated; no submission date yet proposed by the notifier, refer to point 4.2.2).
- Notifier to submit a refinement of the long term risk to granivorous birds (proposed by EFSA; relevant for the use as a seed treatment in cereals if the risk is assessed according to the latest guidance document (SANCO/4145/2000), no submission date proposed by the notifier; refer to point 5.1)
- A study or at least a solid argumentation regarding the effects of the metabolite 2-chlorophenol on aquatic organisms. This data requirement is proposed by EFSA and has not been discussed in an EPCO experts' meeting (relevant for all representative uses evaluated; no submission date yet proposed by the notifier; refer to point 5.2)
- A study or at least a solid argumentation regarding the effects of the metabolite 2-chlorophenol on earthworms. This data requirement is proposed by EFSA and has not been discussed in an EPCO experts' meeting (relevant for all representative uses evaluated; no submission date yet proposed by the notifier; refer to point 5.5)
- A study or at least a solid argumentation regarding the effects of the metabolite 2-chlorophenol on soil micro-organisms. This data requirement is proposed by EFSA and has not been discussed in an EPCO experts' meeting (relevant for all representative uses evaluated; no submission date yet proposed by the notifier; refer to point 5.7)

CONCLUSIONS AND RECOMMENDATIONS

Overall conclusions

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

wheat, rye and barley at application rate up 200 g fluoxastrobin per hectare. An Annex III dossier for a representative seed treatment containing fluoxastrobin was submitted and evaluated. However, owing to issues relating to the other active substances present in the formulation used for seed treatment, it was not possible to complete overall the risk assessment.
Fluoxastrobin can be used only as fungicide. The representative formulated product for the evaluation was "HEC 5725 EC 100", an emulsifiable concentrate (EC).

Adequate methods are only available to monitor the compounds given in the respective residue definitions for food and air. Only single methods for the determination of residues are available since a multi-residue-method like the German S19 or the Dutch MM1 is not applicable due to the nature of the residues.
Sufficient analytical method as well as methods and data relating to physical, chemical and technical properties are available to ensure that quality control measurements of the plant protection product are possible.

Fluoxastrobin is rapidly and nearly completely absorbed from the gastrointestinal tract and widely distributed within the body of the treated animals at generally low concentrations. The highest concentrations are detected in liver, kidneys and bladder as well as in the gastrointestinal tract. No accumulation in the body is observed. The major route of excretion in rats was biliary and faecal. The metabolism is extensive and 50 metabolites are identified. The acute toxicity of fluoxastrobin is low; it is not a skin or an eye irritant. No skin sensitisation potential was observed in a study with a batch containing 3.5 % of impurities of the technical specification for which approval is sought.
The liver is the main target organ in all tested species (rats, mice and dog). The overall short term NOAEL in dogs is 3 mg/kg bw/day in the 1-year dog study at the 90-day time point, also supported by the 90-day dog study. The NOAEL in the 1-year dog study (time point 12 months) is 1.5 mg/kg bw/day.
There is no evidence of genotoxic activity due to the test material or to the impurities.
There is no evidence of a substance-related oncogenic or reproductive effects in rats and mice. The relevant NOAEL for long term toxicity and carcinogenicity is 35 mg/kg bw/day in rats. The NOAEL for reproduction is 742-764 mg/kg bw/day and the parental NOAEL is 74-87 mg/kg bw/day. The NOAEL for maternal toxicity in rabbits is 25 mg/kg bw/day and the developmental is 100 mg/kg bw/day. In the rat the maternal and developmental NOAELs are 1000 mg/kg bw/day).
Fluoxastrobin gave no evidence of substance-related neurotoxicity. Metabolite 48 was not mutagenic in Ames test. It is not considered a relevant metabolite for groundwater risk assessment based on consumer risk assessment (0.3% of fluoxastrobin ADI).
Studies in rats and mice did not reveal any adverse immunotoxic effects. Fluoxastrobin resulted in reduced phosphate absorption in the intestine and in reduced renal excretion of phosphate and renal hyper-excretion of calcium. No adverse medical effects have been reported for manufacturing plant personnel.
The **ADI is 0.015 mg/kg bw/day,** the **AOEL is 0.03 mg/kg bw/day,** and the **ARfD is 0.3 mg/kg bw** with a 100-fold assessment factor applied.

A dermal absorption value for of 4% considered for operator risk assessment of undiluted and in-use dilutions of HEC 5725 EC100. The estimated operator exposure is below the AOEL without PPE (34%), according to the German model. According to calculations with UK POEM, gloves have to be worn when handling the concentrate (in addition to a faceshield due to the classification of the product as an eye irritant) and when handling contaminated surfaces (29% of the AOEL). Worst case estimates using the German worker re-entry model together with published transfer coefficient data, indicate that the level of systemic exposure for unprotected workers entering treated cereal crops for inspection purposes is below the AOEL, as well as the level of systemic bystander exposure to fluoxastrobin (0.5% of the proposed systemic AOEL).

Applied to wheat plants by foliar application following a seed treatment fluoxastrobin itself and its *Z*-isomer was the major residue found at harvest in straw and in grain accounting for about 86% and 80% of the total residue, respectively. Some metabolites found in plants were not observed in rat metabolism. However, due to their insignificant levels (<0.01 mg/kg) they were considered being of no concern in grain, whereas in straw some non-rat metabolites, e.g. 2-chlorophenol (M82) and its glycoside (M84) are expected to be present at significant levels. However, M82 was also seen in livestock metabolism studies with fluoxastrobin, but others were not and their toxicity was not tested further. Depending on the soil, fluoxastrobin was shown to be highly persistent in soil and hence it was present in rotational crops at plant back intervals up to 328 days as the major residue. Decline of fluoxastrobin residues under processing conditions does not occur.
Fed to ruminants and poultry, fluoxastrobin was intensively metabolised resulting in a comparable pattern to that observed in rat metabolism, with the exception of some metabolites, that were not specifically found in the rat, but not considered to be of concern due to insignificant levels (<0.01 mg/kg). In a feeding study levels of relevant compounds (fluoxastrobin, *Z*-isomer, metabolite M55) in edible animal matrices were analysed, and MRLs have been proposed.
The chronic dietary exposure assessment for consumers based on the representative GAP on cereals indicated that for all consumer subgroup the intake was less then 10% of the proposed ADI. The short term exposure of all considered consumer subgroups from individual commodities, based on consumption data of UK consumers, was all below 1% of the proposed ARfD. In an assessment of possible consumer exposure and consumer risk due to intake of metabolite M48 from drinking water the margin of safety was shown to be sufficient.

Under aerobic conditions fluoxastrobin yield the major metabolite M48-*E* and 2-chlorophenol in soil. No significant formation of the *Z* isomer of fluoxastrobin is observed under dark conditions. Mineralization was generally low. Unextractable residues reached a maximum of 71 % AR after 120 d in one of the soils but were below 70 % in the rest of experiments.
In an anaerobic water sediment study major metabolite M40 is formed and was identified as a potential major anaerobic metabolite in soil under anaerobic conditions. However, for the representative uses proposed, extended periods of anaerobic conditions are not expected.
Z-isomer of fluoxastrobin was identified as the major soil photolysis metabolite of fluoxastrobin.

Any of the laboratory soil studies uses fluoxastrobin labelled at the chlorophenyl ring. As a result of the cleavage of the molecule this ring will be released as 2-chlorophenol (expected worst case maximum amount equivalent to 49.2 %, see EFSA addendum of 26 July, 2005). The microbiologically driven degradation of 2-chlorophenol in soil was supported with a number of studies from the open scientific literature.

Field dissipation trials in typical agricultural regions of Europe are available. In field trials the *Z* isomer of fluoxastrobin was measured at up to 19 % - 22 %. The EPCO experts' meeting on fate and behaviour in the environment (EPCO 12, September 2004) agreed that *Z*-isomer of fluoxastrobin should be included in the residue definition in soil and assessed for their potential ecotoxicological relevance.

Persistence of fluoxastrobin in soil may be very variable. Fluoxastrobin may behave as a moderate to high persistent compound ($DT_{50\ lab\ 20\ °C}$ = 12 d to 356 d). Also a high variability on the rate of degradation was observed in field studies ($DT_{50\ field}$ = 16 d – 119 d).

Three reliable values were obtained for the half life of metabolite M48 indicating that this metabolite is moderate to medium persistent in soil ($DT_{50\ lab\ 20\ °C}$ = 34 d – 100 d).

Anaerobic metabolite M40 is moderately persistent in soil under aerobic conditions ($DT_{50\ lab\ 20\ °C}$ = 11 d – 25 d).

Data available from open scientific literature show that the aerobic soil metabolite 2-chlorophenol is very low to moderately persistent in soil (DT_{50} = 0.6 d – 23 d).

PEC soil were calculated from peak concentration after four subsequent seasons with a seed treatment and two foliar applications per season using the worst case field half life (DT_{50} = 119 d) for the parent compound. Maximum PEC for M48 provided in the DAR is based on worst case field formation of 6.3 %. Maximum PEC soil for metabolite 2-chlorophenol has been calculated by EFSA (see EFSA addendum of 26 July, 2005).

Fluoxastrobin may be classified as low to medium mobile (Koc = 424 – 1582 mL / g), M48 as medium to very high mobile (Koc = 14 – 181 mL / g) and M40 high to very high mobile (Koc = 37 – 87 mL / g). The rapporteur Member State identified a Koc pH dependence for fluoxastrobin with a reduced adsorption with increasing soil pH. No adsorption / desorption data is available for metabolite 2-chlorophenol. This may be necessary to address the potential groundwater contamination and has been identified as a new data requirement by EFSA.

Fluoxastrobin is stable to hydrolysis at all environmental relevant pHs. Aqueous photolysis contributes to the aqueous dissipation of fluoxastrobin. The main photolysis metabolites are: *Z* isomer of fluoxastrobin, M36 and M56.

No studies on ready biodegradability of fluoxastrobin are available and fluoxastrobin was proposed to be non ready biodegradable by the experts meeting.

Two aerobic water sediment systems at 20 °C under dark conditions were investigated. Only M48-*E* was seen above 10 % AR in the water phase. Concomitant formation of 2-chlorphenol at levels above 10 % cannot be precluded. Degradation of fluoxastrobin was slow in both systems ($DT_{50\ whole\ system}$ = 144 d – 188 d). Dissipation from the water phase was mainly due to partition in to the sediment ($DT_{50\ water}$ = 25.6 d – 42.1 d). Mineralization was very low (CO_2: max 2.9 % AR after 122 d, end of the study). Bound residues increased during the study to a maximum of 12.7 % AR.

Additionally, a study with two irradiated aerobic water sediment at 25 °C systems is available. Formation of the metabolite *Z*-isomer of fluoxastrobin was observed. Contribution of photodegradation to the dissipation of fluoxastrobin from the water phase in these systems is not significant, probably due to the rapid adsorption to the sediment.

PECsw and PECsed were provided by the applicant assuming spray drift from two 200 g/ha applications with 14 days interval taking as basis the worst case dissipation DT_{50} observed in dark water sediment study. Spray drift initial PECsw for the metabolite M48-*E* was calculated by the rapporteur Member State based on the maximum amount of this metabolite observed in the water sediment systems. The rapporteur Member State also provided PECsw for drainage based on their national scheme. Potential loadings to surface water through run off were not considered in the assessment presented in the DAR. Due to the fact that fluoxastrobin may be high persistent in soil, potential surface water contamination through drainage and run off may not be excluded; therefore, a comprehensive assessment taking into account spray drift, run-off, drainage and effectiveness of potential mitigation measures to reduce surface water contamination is necessary to finalize the risk assessment of the EU representative uses.

PECgw of Fluoxastrobin and the metabolite M48-*E* were estimated using FOCUS-PELMO 1.1.1. Calculated concentrations of Fluoxastrobin at 1 m depth were negligible. However, metabolite M48-*E* exceeds the trigger 0.1 µg /L in eight of the nine scenarios when dependence of the adsorption Koc with the soil pH is taken into account. It is noted that for six of the scenarios the level of 0.75 µg /L is also exceeded by metabolite M48-*E*. Relevance assessment has been performed for this metabolite (see table in section 6 of this conclusion).

Potential groundwater contamination by soil metabolite *Z*-isomer of fluoxastrobin is not addressed in the DAR and has not been discussed during the Peer Review. Since physical and chemical properties and behaviour in the environment of this metabolite is expected to be very similar to the parent, EFSA considers that the results of the exposure assessment made for fluoxastrobin may be applied to the *Z*-isomer.

Potential groundwater contamination by soil metabolite 2-chlorophenol is not addressed in the DAR and has not been discussed during the Peer Review. EFSA identified a new data requirement since potential groundwater contamination of major soil metabolite 2-chlorophenol needs to be addressed.

Concentration of fluoxastrobin in air is expected to be negligible due to low volatility and short half life in air for reaction with OH radicals.

In the section on ecotoxicology only the risk to non-target organisms from the representative use in cereals as a spray application was assessed. No risk assessment for the representative use as a seed treatment in cereals is available in the DAR.

It should be noted that the assessment in the DAR is based on a pilot plant production. Since then the production process has been modified and optimised. Therefore, a new material accountability study and a new five batch analysis have been performed. The new resultant specification was supported by additional toxicological data, which have been peer-reviewed and accepted. An appropriate assessment with respect to ecotoxicology is still outstanding.

The risk to bees, non-target terrestrial plants and biological methods for sewage treatment is low with respect to fluoxastrobin and the metabolites for the use as a spray application in cereals.

The risk to herbivorous birds and mammals can be regarded as low for the representative use of fluoxastrobin as a spray application if the risk was calculated using residue data as outlined in EPPO (1992). EFSA made a risk assessment available according to the latest guidance document on birds and mammals (SANCO/4145/2000). According to this assessment (see addendum by EFSA) the risk to mammals can be regarded as low and also the acute, short and long term risk for insectivorous and herbivorous birds as well as the acute and short term risk to granivorous birds from the representative uses evaluated can be regarded as low. But a long term risk to granivorous birds is observed (TER= 1.79 according to SANCO/4145/2000). Therefore EFSA proposes a data requirement for the notifier to submit a refinement of the long term risk to granivorous birds for the use as a seed treatment in cereals if the risk is assessed according to the latest guidance document (SANCO/4145/2000).
A high risk is identified to *Americamysis bahia* (being the most sensitive aquatic organisms), which requires consideration of appropriate risk mitigation measures. A bufferzone of 15 metres is needed to respect the Annex VI trigger value for the long term risk to aquatic organisms for the use of fluoxastrobin as a spray application in cereals. It was noted by the EPCO 13 Expert meeting on ecotoxicology that additional chronic invertebrate data are available. The meeting agreed that some lowering of the chronic uncertainty would be acceptable in this case and that these additional data may be used to refine the risk assessment at MS level. Furthermore the meeting decided to send a generic question on lowering the uncertainty factor by using additional chronic species sensitivity data to the PPR Panel. This generic question was forwarded to the PPR Panel by EFSA. The opinion of the Panel is still awaited. The risk of the metabolite M 48 to aquatic organisms is considered to be low. The EPCO 13 Expert meeting on ecotoxicology decided that based on biological screening data, data on Daphnia and some mammalian data that it is unlikely that the *Z*-isomer is of greater toxicity than the *E*-isomer. It is noted by EFSA that also the metabolite 2-chlorophenol is considered as a major metabolite by the section on Fate and behaviour. No studies with this metabolite are available and therefore EFSA proposes that a study or at least a solid argumentation regarding the effects of the metabolite 2-chlorophenol on aquatic organisms should be made available. The need for this data was not discussed at an EPCO experts' meeting.
The risk to non-target arthropods was discussed at the EPCO 13 Expert meeting on ecotoxicology. The meeting decided that based on the available data, population recovery/recolonisation in-field would be possible within one year. Therefore the meeting agreed that the risk to non-target arthropods is addressed for the representative use of fluoxastrobin as a spray application.
The risk to soil micro- and macro-organisms, including earthworms is low with respect to fluoxastrobin and the metabolites M48 and M40 for the use of fluoxastrobin as a spray application in cereals. The EPCO 13 Expert meeting on ecotoxicology decided that it is unlikely that the *Z*-isomer is of greater toxicity than the *E*-isomer (see above). It is noted by EFSA that also the metabolite 2-chlorophenol is considered as a major metabolite by the section on Fate and behaviour. No studies with this metabolite are available and therefore EFSA proposes that a study or at least a solid

argumentation regarding the effects of the metabolite 2-chlorophenol on earthworms and soil micro-organisms should be made available. The need for this data was not discussed at an EPCO experts' meeting.

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

- The use of a faceshield for operators, due to the classification of the product as an eye irritant, should be taken into consideration.
- Appropriate risk mitigation measures (e.g. a 15 meter no spray bufferzone) are required with regard to aquatic organisms (refer to point 5.2).
- Straw data demonstrated that metabolites of unknown toxicity (non-rat metabolites) were present at harvest in straw samples, partially at significant levels. Restriction for feeding of straw is recommended or if straw is intended for use as animal feeding stuff the issue of toxicity tests on non-rat metabolites should be addressed further. (refer to points 2.8 and 3.1.1)

Critical areas of concern

- No analytical method for enforcement purposes is available to determine the metabolite M48-*E* in groundwater. Provided that 2-chlorophenol will be included in the residue definitions for soil and water (ground and surface) also no enforcement method would be available.
- The operator risk assessment has been conducted only on the representative use in cereals as a spray application. No risk assessment for the representative use as a seed treatment in cereals is available in the DAR.
- The use of a faceshield for operators (for foliar spraying in cereals), due to the classification of the product as an eye irritant, should be taken into consideration.
- In straw, individual non-rat metabolites (M34, M39, M40, M42, M70, M82, M84) reached levels above 0.1 mg/kg, relating to 1N application rate. No toxicity tests, neither *in vivo* nor *in vitro,* were provided to define their toxicity. Therefore, they should be considered as toxicologically relevant, unless new data are made available.
- In the section on ecotoxicology only the risk to non-target organisms from the representative use in cereals as a spray application was assessed. No risk assessment for the representative use as a seed treatment in cereals is available in the DAR.
- It should be noted that the assessment in the DAR is based on a pilot plant production. Since then the production process has been modified and optimised. Therefore, a new material accountability study and a new five batch analysis have been performed. The new resultant specification was supported by additional toxicological data, which have been peer-reviewed and accepted. An appropriate assessment with respect to ecotoxicology is still outstanding.
- If the risk to birds is calculated according to the latest guidance document (SANCO/4145/2000) a long term risk to granivorous birds is observed (TER= 1.79 according to SANCO/4145/2000). Therefore EFSA proposes a data requirement for the notifier to submit a refinement of the long term risk to granivorous birds for the use as a seed treatment in cereals if the risk is assessed according to the latest guidance document (SANCO/4145/2000).

- A high risk to aquatic organism is identified which requires consideration of appropriate risk mitigation measures. A bufferzone of 15 metres is needed to respect the Annex VI trigger value for the long term risk. It was noted by the EPCO experts' meeting on ecotoxicology that additional chronic invertebrate data are available. The meeting agreed that some lowering of the chronic uncertainty would be acceptable in this case and that these additional data may be used to refine the risk assessment at MS level. Furthermore the meeting decided to address a generic question on lowering the uncertainty factor by using additional chronic species sensitivity data to the PPR Panel. This generic question was forwarded to the PPR Panel by EFSA; the opinion of the Panel is still pending.

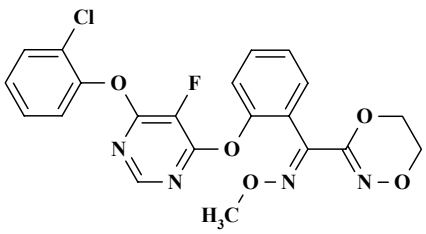
APPENDIX 1 – LIST OF ENDPOINTS FOR THE ACTIVE SUBSTANCE AND THE REPRESENTATIVE FORMULATION

(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) ‡	Fluoxastrobin
Function (e.g. fungicide)	Fungicide
Rapporteur Member State	UK
Co-rapporteur Member State	--

Identity (Annex IIA, point 1)

Chemical name (IUPAC) ‡	(*E*)-{2-[6-(2-chlorophenoxy)-5-fluoropyrimidin-4-yloxy]phenyl}(5,6-dihydro-1,4,2-dioxazin-3-yl)methanone *O*-methyloxime
Chemical name (CA) ‡	(E) Methanone, [2-[[6-(2-chlorophenoxy)-5-fluoro-4-pyrimidinyl]oxy]phenyl](5,6-dihydro-1,4,2-dioxazin-3-yl)-, O-methyloxime (9CI)
CIPAC No ‡	746
CAS No ‡	361377-29-9
EEC No (EINECS or ELINCS) ‡	not allocated
FAO Specification ‡ (including year of publication)	not allocated
Minimum purity of the active substance as manufactured ‡ (g/kg)	940 g/kg
Identity of relevant impurities (of toxicological, environmental and/or other significance) in the active substance as manufactured (g/kg)	None of the impurities are considered to be of toxicological, environmental and/or other significance.
Molecular formula ‡	$C_{21}H_{16}ClFN_4O_5$
Molecular mass ‡	458.8 g/mol
Structural formula ‡	

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

Physical-chemical properties (Annex IIA, point 2)

Melting point (state purity) ‡	103-108 °C (99.5%)
Boiling point (state purity) ‡	Estimated to be 497 °C. (Pure active substance (99.5%) decomposes at temperatures above 230 °C)
Temperature of decomposition	>230 °C (99.5%)
Appearance (state purity) ‡	White solid (98.5%)
Relative density (state purity) ‡	1.422 (99.5%)
Surface tension	68 mN/m (ca 90% saturated solution)
Vapour pressure (in Pa, state temperature) ‡	5.6 x 10^{-10} Pa at 20 °C
Henry's law constant (Pa m^3 mol^{-1}) ‡	1 x 10^{-7} Pa m^3 /mol at 20 °C
Solubility in water ‡ (g/l or mg/l, state temperature)	pH 4: 2.43 mg/l at 20 °C pH 7: 2.29 mg/l at 20 °C pH 9: 2.27 mg/l at 20 °C
Solubility in organic solvents ‡ (in g/l or mg/l, state temperature)	*n*-heptane 0.04g/l at 20 °C 1-octanol 1.1g/l at 20 °C 2-propanol 6.7g/l at 20 °C xylene 38g/l at 20 °C polyethylene glycol 120g/l at 20 °C ethyl acetate >250g/l at 20 °C acetonitrile >250g/l at 20 °C acetone >250g/l at 20 °C Dichloromethane >250g/l at 20°C Dimethlsulfoxide >250g/l at 20°C
Partition co-efficient (log POW) ‡ (state pH and temperature)	log P_{ow} = 2.86 at 20 °C Range of pH's were not looked at as fluoxastrobin does not dissociate
Hydrolytic stability (DT50) ‡ (state pH and temperature)	Stable to hydrolysis for at least 7 days at pH 4-9 and 50 °C. Applicant stated that this indicated that at environmental pH's and temperatures, fluoxastrobin is hydrolytically stable
Dissociation constant ‡	Fluoxastrobin has no acid or basic properties in aqueous solutions. It is therefore impossible to specify dissociation constants of the active ingredient in water
UV/VIS absorption (max.) ‡ (if absorption > 290 nm state ε at wavelength)	UV absorb 250 nm (ε = 19358 l mol^{-1} cm^{-1}). No UV absorbance above 290 nm.
Photostability (DT50) ‡ (aqueous, sunlight, state pH)	31 days at pH 7 in sterile aqueous buffered solution, based on sunlight in Athens in June

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

Quantum yield of direct phototransformation in water at Σ > 290 nm ‡	0.00098 (*E*-isomer) 0.00089 (Sum of *E* and *Z*-isomers)
Flammability ‡	Not considered highly flammable
Explosive properties ‡	Non-explosive

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

List of representative uses evaluated*

Crop and/ or situation (a)	Member State or Country	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 (n)	water L/ha min max	kg a.s./ha min max		
Wheat, rye, barley	EU North South	not defined	F	Rusts, Leave spot. Pyren. teres, Powd. mildew, Rhynchospor., Septoria	EC	100 g/L	overall spray	start 26 up to BBCH 69	1 – 2 #	14 days ref. to growth stage	0.025 – 0.1	200 - 400	0.1 - 0.2	35	# number application depends on disease incidence
Wheat, rye, triticale	EU North South	not defined	F	Fusarium nivale, Fusarium spp., Smut, Bunt	FS	37.5 HEC 37.5 JAU 5 Teb. g/L	seed treat-ment	pre sowing	1	n.a. (0)	n.a.	up to 500 ml seed dressing solution[1]	(g a.s./dt seed) Fluoxastrobin (7.5) Prothioconazole (7.5) Tebuconazole(1) [2]	n.a.	(1) dilution with water 1:1 to 1:1.5, in small scale facilities up to 1:4 (2) up to 230 kg seed/ha

HEC = fluoxastrobin, JAU = prothioconazole and Teb. = tebuconazole

Remarks:	(a)	For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)	(i)	g/kg or g/L
	(b)	Outdoor or field use (F), glasshouse application (G) or indoor application (I)	(j)	Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
	(c)	*e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds		
	(d)	*e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)	(k)	The minimum and maximum number of application possible under practical conditions of use must be provided
	(e)	GCPF Codes - GIFAP Technical Monograph No 2, 1989		
	(f)	Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench	(l)	PHI - minimum pre-harvest interval
	(g)	All abbreviations used must be explained	(m)	Remarks may include: Extent of use/economic importance/restrictions
	(h)	Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated	(n)	product concentration of spray liquid

(*) Uses for which risk assessment could not been concluded due to lack of essential data are marked grey.

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

Appendix 1.2: Methods of Analysis

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

Technical as (principle of method)	Fluoxastrobin was determined in the technical active substance by HPLC-UV and in the plant protection products by HPLC-UV and GC-FID. Satisfactory methods were submitted for the determination of impurities in the technical active substance.
Impurities in technical as (principle of method)	Impurities in technical active substance was determined by HPLC-UV.
Plant protection product (principle of method)	Fluoxastrobin was determined in the plant protection products by HPLC-UV and GC-FID.

Analytical methods for residues (Annex IIA, point 4.2)

Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes)

Fluoxastrobin residues (fluoxastrobin *E* and *Z*) in cereals and beer products were determined by extracted with acetone/water or methanol/water and the resulting extracts cleaned up on solid phase extraction column and the resulting eluants analysed by HPLC-MS/MS. The limits of determination were:

Matrix	analyte	LOQ (mg/kg)
Barley grain	E + Z	0.02
Barley grain	E	0.02
Barley grain	Z	0.02
Beer	E + Z	0.05
Beer	E	0.05
Beer	Z	0.05
Wheat grain	E + Z	0.02
Wheat grain	E	0.02
Wheat grain	Z	0.02

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

Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes)

Fluoxastrobin residues (fluoxastrobin *E* and *Z* and its metabolite phenoxy-hydroxy-pyrimidine [M55]) in animal products were determined by extracted with acetonitrile/water and the resulting extracts cleaned up on solid phase extraction column and the resulting eluants analysed by HPLC-MS/MS. The limits of determination were:

Matrix	analyte	LOQ (mg/kg)
Cattle fat	E	0.01
Cattle fat	Z	0.01
Cattle fat	M55	0.01
Cattle kidney	E	0.02
Cattle kidney	Z	0.02
Cattle kidney	M55	0.02
Cattle muscle	E	0.01
Cattle muscle	Z	0.01
Cattle muscle	M55	0.01
Milk	E	0.01
Milk	Z	0.01
Milk	M55	0.01

Soil (principle of method and LOQ)

Fluoxastrobin residues (fluoxastrobin *E* and *Z*, des-chlorophenyl-fluoxastrobin [M48] (and fluoxastrobin carboxylic acid [M40]) in soil were determined by extracted with acetonitrile/water and the resulting extracts analysed by HPLC-MS/MS. The limits of determination were:

Matrix	analyte	LOQ (mg/kg)
Soil	E	0.005
	Z	0.005
	M48	0.005
	M40	0.0045

Water (principle of method and LOQ)

Fluoxastrobin residues (fluoxastrobin *E* and *Z*) in water were determined by direct injection into a HPLC-MS/MS). The limits of determination were:

Matrix	analyte	LOQ (mg/kg)
Surface water	E	0.05 µg/l
	Z	0.05 µg/l

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

Air (principle of method and LOQ)	Fluoxastrobin residues fluoxastrobin (E isomer only) in air were determined by solid phase extraction and the resulting eluants analysed by HPLC-UV-DAD. The limit of determination was 4 $\mu g/m^3$.
Body fluids and tissues (principle of method and LOQ)	No methods of analysis were submitted or required, as fluoxastrobin is not classified as toxic.

Classification and proposed labelling (Annex IIA, point 10)

with regard to physical/chemical data	None

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

Appendix 1.3: Impact on Human and Animal Health

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

Rate and extent of absorption ‡	80—92% within 24-30h (ca. 80% biliary, remainder in urine)
Distribution ‡	Highest concentrations in liver, kidneys, bladder and gastrointestinal tract
Potential for accumulation ‡	No evidence of accumulation
Rate and extent of excretion ‡	84-100% within 48h (mostly via bile)
Metabolism in animals ‡	Extensively metabolised (< 10% of administered dose recovered as parent at low dose). 50 metabolites identified.
Toxicologically significant compounds ‡ (animals, plants and environment)	Fluoxastrobin. Metabolite 48 is not considered as toxicologically relevant; metabolites M34, M39, M40, M41, M57, M70, M72 and M82 are present in wheat but not in rat metabolism: no toxicity data available – considered as toxicologically relevant

Acute toxicity (Annex IIA, point 5.2)

Rat LD50 oral ‡	> 2000 mg/kg bw
Rat LD50 dermal ‡	> 2000 mg/kg bw
Rat LC50 inhalation ‡	> 5 mg/L
Skin irritation ‡	Non-irritant
Eye irritation ‡	Slight but not classifiable
Skin sensitization ‡ (test method used and result)	Non-sensitiser (Magnusson and Kligman) in test with HEC 5725 of high purity (98.1% pure) and HEC 5725 (93.6%).

Short term toxicity (Annex IIA, point 5.3)

Target / critical effect ‡	Reduced body weight gain and increased serum alkaline phosphatase (critical effects in dogs) Liver (main target organ in dogs, mice and rats) Kidney/urethra/bladder lesions (at high dose in rats)
Lowest relevant oral NOAEL / NOEL ‡	90-day, dog: 3 mg/kg bw/day based on two 90-day dog and 90 day time point in 1-year dog studies 1-year, dog: 1.5 mg/kg bw/d
Lowest relevant dermal NOAEL / NOEL ‡	>1,000 mg/kg bw/d

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

Lowest relevant inhalation NOAEL / NOEL ‡	No data submitted (none required)

Genotoxicity ‡ (Annex IIA, point 5.4)

	Not genotoxic

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

Target/critical effect ‡	Reduced body weight gain in rats (= the critical effect) Liver (target organ in rats and mice) Altered calcium and phosphate metabolism (rats)
Lowest relevant NOAEL / NOEL ‡	2-year, rat: 500 ppm (35 mg/kg bw/day)
Carcinogenicity ‡	No carcinogenic potential

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction target / critical effect ‡	No adverse effects on reproductive outcome. Developmental effects (reduced body weight gain, delayed development, reduced weight of thymus and spleen) at parentally toxic dose
Lowest relevant reproductive NOAEL / NOEL ‡	Reproductive: 742-764 mg/kg bw/day Parental: 74-87 mg/kg bw/day.
Developmental target / critical effect ‡	Slight dilation of brain ventricles in rabbits at maternal toxic dose Minimal evidence for retarded skeletal ossification in rats (possible presence of altered maternal Ca/P homeostasis not investigated in this study). No classification necessary.
Lowest relevant developmental NOAEL / NOEL ‡	Developmental and maternal (rat): 1000 mg/kg bw/d Maternal (rabbit): 25 mg/kg bw/day Developmental (rabbit): 100 mg/kg bw/day

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

.....	Not neurotoxic in acute and subchronic studies in rats

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

Other toxicological studies ‡ (Annex IIA, point 5.8)

.....	Specific investigations in rats and mice did not show any immunotoxic effects. In rats, phosphate and calcium homeostasis disturbed as a result of reduced phosphate absorption from gut. Relative phosphate deficiency counter-regulated by reduced renal excretion of phosphate and renal hyper-excretion of calcium. At high doses, increased calcium excretion and increased urinary pH led to calculi formation and other lesions of urinary system.
Impurities	Impurities 7, 15, 20, 21 and 22: rat oral LD50 >2500 mg/kg bw, not mutagenic in Ames test Impurity 23: rat oral LD50 >300 <500 mg/kg bw, not mutagenic in Ames test
Metabolites	Metabolite 48: not mutagenic in Ames test. No other toxicological data available, however present in rat metabolism to 10-20% of the administered dose.

Medical data ‡ (Annex IIA, point 5.9)

.....	No detrimental effects on health in manufacturing personnel

Summary (Annex IIA, point 5.10)

	Value	Study	Safety factor
ADI ‡	0.015 mg/kg bw/day	Dog, 1-year study	100
AOEL ‡	0.03 mg/kg bw/day	Dog, 90-day and 90-day time point from 1-year studies	100
ARfD ‡ (acute reference dose)	0.3 mg/kg bw	Dog, first week of 90-day and 1-year studies	100

Dermal absorption (Annex IIIA, point 7.3)

HEC 5725 EC 100 (for use as a spray application in cereals)	4% for fluoxastrobin from the HEC5725 EC 100 formulation (concentrate and in-use dilution), based on an *in vivo* monkey study.

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

Acceptable exposure scenarios (including method of calculation)

The operator risk assessment has been conducted only on the representative use in cereals as a spray application. No risk assessment for the representative use as a seed treatment in cereals is available in the DAR.

Operator	HEC 5725 EC 100 is an aqueous suspension (containing. 1.5 mg a.s./ml of diluted formulation) with a maximum application rate of 200 g fluoxastrobin/ha. Estimates using the German model indicate that the level of systemic exposure to fluoxastrobin for an unprotected operator is below the AOEL of 0.03 mg/kg bw/day (34%). UK POEM estimates predict that the level of systemic exposure to fluoxastrobin is equivalent to 29% of the AOELwhen suitable protective gloves are worn when handling the concentrate (in addition to a faceshield due to the classification of the product as an eye irritant) and when handling contaminated surfaces.
Workers	Worst case estimates using the German worker re-entry model together with published transfer coefficient data, indicate that the level of systemic exposure is equivalent to 8% of the proposed systemic AOEL of 0.03 mg/kg bw/day.
Bystanders	On the basis of generic simulated monitoring data, the level of systemic bystander exposure to fluoxastrobin is equivalent to 0.5% of the proposed systemic AOEL of 0.03 mg/kg bw/day.

Classification and proposed labelling (Annex IIA, point 10)

with regard to toxicological data	None

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

Appendix 1.4: Residues

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

Plant groups covered	Cereals
Rotational crops	Wheat, Turnip and Swiss Chard
Plant residue definition for monitoring	Fluoxastrobin and Z-isomer (cereals only)
Plant residue definition for risk assessment	Fluoxastrobin and Z-isomer (cereals only)
Conversion factor (monitoring to risk assessment)	1

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

Animals covered	Lactating goat and hen
Animal residue definition for monitoring	Sum of fluoxastrobin, Z-isomer and the phenoxy-hydroxy-pyrimidine metabolite (M55) expressed as fluoxastrobin
Animal residue definition for risk assessment	Sum of fluoxastrobin, Z-fluoxastrobin and the phenoxy-hydroxy-pyrimidine metabolite (M55) expressed as fluoxastrobin
Conversion factor (monitoring to risk assessment)	1
Metabolism in rat and ruminant similar (yes/no)	Yes
Fat soluble residue: (yes/no)	No, based on partition coefficient.

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

.....	No data were submitted or required, due to residues of parent and individual metabolites in rotational crops being less than 0.1 mg/kg in the rotational crop metabolism study, with the exception of fluoxastrobin and fluoxastrobin-4-hydroxyphenyl in wheat straw planted in 30 and 162 aged soil. However, as fluoxastrobin is for use on cereals, it is unlikely that residues of fluoxastrobin in the soil would contribute significantly to the residue in following cereal crops treated with fluoxastrobin for the following reasons: the metabolism study was conducted at 2N radiolabelled fluoxastrobin was applied to bare soil instead of a crop the proposed application being three treatments and not one as in the metabolism study – seedtreatment

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

	(12 months before following crop planted) and two foliar treatments at GS 32 (5 months year before following crop planted) and 69 (3 months before following crop planted).

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

.....	Residues of fluoxastrobin are stable for up to 24 months in tomatoes, lettuce, wheat forage, wheat grain, wheat straw and potatoes.

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

Intakes by livestock ≥ 0.1 mg/kg diet/day:	Ruminant: yes	Poultry: no	Pig: no
Muscle	Mean residue = 0.01 mg/kg Highest residue = 0.01 mg/kg	-	-
Liver	Mean residue = 0.02 mg/kg Highest residue = 0.02	-	-
Kidney	Mean residue = 0.04 mg/kg Highest residue = 0.05 mg/kg	-	-
Fat	Mean residue = 0.01 Highest residue = 0.02	-	-
Milk	Mean residue = 0.01 Highest residue = 0.01	-	-
Eggs	-	-	-

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 (a)	Recommendation/comments	MRL	STMR (b)
Wheat and rye Grain	N S	8x<0.02 7x<0.02, 1x0.02	Acceptable	0.05	< 0.02
Wheat straw	N S	0.14, 0.28, 0.33, 0.61, 0.64, 0.79, 0.92, 0.97 0.50, 0.61, 0.70, 0.71, 0.81, 1.2, 2.7, 6.0			0.63 0.76

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

Crop	Northern or Mediterranean Region	Trials results relevant to the critical GAP (a)	Recommendation/comments	MRL	STMR (b)
Barley grain	N S	3x<0.02, 1x0.02, 3x0.03, 1x0.04 1x<0.02, 1x0.02, 1x0.05, 1x0.24, 1x0.27	Acceptable	0.5	0.05
Barley straw	N S	0.14, 0.15, 0.26, 0.37, 0.5, 1.1, 1.7, 2.8 0.25, 0.79, 2.6, 4.7, 11			0.44 2.6

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

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

ADI	0.015
TMDI (European Diet) (% ADI)	< 3%[6] (adults)
NEDI (% ADI)	< 10%[7] (including infant, toddler)
Factors included in NEDI	STMRs
ARfD	0.3
Acute exposure (% ARfD)	< 1%

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

Crop/processed crop	Number of studies	Transfer factor	% Transference *
Barley/Barley rub	2	3	
Barley/Pearl barley	2	1*	
Barley/Malted sprout	2	1.6	
Barley/Brewers malt	2	1.6	
Barley/Brewers grain	2	1.5	
Barley/Hops draft	2	1*	
Barley/Brewers yeast	2	1*	
Barley/Beer	2	1*	

[6] intake of M48 through drinking water not included, estimated <1% ADI of fluoxastrobin for adults
[7] intake of M48 through drinking water not included, estimated <4% ADI of fluoxastrobin for infant/toddler

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

Limit of determination (0.05 mg/kg) was greater than the residue in the barley (0.03-0.04 mg/kg)
* Calculated on the basis of distribution in the different portions, parts or products as determined through balance studies

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

Commodity	Proposed MRL (mg/kg)
Wheat	0.05
Barley	0.5
Rye	0.05
Milk	0.02
Meat	0.02
Meat fat	0.05
Kidney	0.1
Liver	0.05

*) LOQ

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

Appendix 1.5: Fate and Behaviour in the Environment

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

Mineralization after 100 days ‡	0.7-10% after 91-98 days ring 3 label (n = 4) 3.6-34.1% after 91 days ring 2 label (n=2)
Non-extractable residues after 100 days ‡	13.4-69.3% after 91-98 days ring 3 label (n = 4) 10.7-34.8 % after 91 days ring 2 label (n=2)
Relevant metabolites - name and/or code, % of applied ‡ (range and maximum)	Major metabolites (>10% AR) M48 18.9-30.2 % after 30-270 days ring 3 label (n = 4) M48 10.3-32.2% after 30-365 days ring 2 label (n=2) 2-chlorophenol: calculated 49.2 % . Estimation based on worst case assumptions.

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

Anaerobic degradation ‡	Non standard anaerobic water sediment study using ring 3 label showed: Negligible mineralisation after 91 days 23.4% unextracted residues after 91 days M40 seen at 12.7% in total system after 120 days
Soil photolysis ‡	2.3-4.4% mineralisation after 15 days irradiation ring 2 label (n = 2) 4.8% mineralisation after 15 days irradiation ring 3 label (n=1) 8.3-8.6% unextracted residue after 15 days ring 2 label (n=2) 10.3% unextracted residue after 15 days ring 3 label (n=1) Z-isomer of fluoxastrobin increased to 17.1% after 15 days ring 3 label and 16.4-22.2% after 15 days ring 2 label. Overall the effect of light on degradation in the environment is likely to be low as the photolytic DT50s of sum of E+Z isomers are not significantly different to dark control DT50s.

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

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

Method of calculation	Parent: first order kinetics (Model Maker) for both lab and field data M48: first order kinetics (ACSL Optimize 1996) for lab data; insufficient data from field 2-chlorophenol: first order kinetic based on data from open scientific literature. Relatively high uncertainty.
Laboratory studies ‡ (range or median, with n value, with r^2 value)	DT_{50lab} (20°C, aerobic): ‡ parent: 12-356 days (n=6, r^2 = 0.87-0.99) M48: 33.8-99.8 days (n=3, r^2 = 0.96-0.99) M40: 10.9-25.1 days (n=3, r^2 = 0.97-0.99) 2-chlorophenol: 0.6-23 days (n = 5, high uncertainty associated to the lack of information on experimental and fitting procedures employed in the published studies) For FOCUSgw modelling for M48- Geometric mean 54.2 days used (Not normalised for soil moisture) DT_{90lab} (20°C, aerobic): ‡ parent: 40-1180 days (n=6, r^2 = 0.87-0.99) M48: 113-333 days (n = 3, r^2 = 0.96-0.99) M40: 36-84 days (n=3, r^2 = 0.97-0.99) DT_{50lab} (10°C, aerobic) parent: ‡ From 20°C aerobic values above as 26.4-783.2 days using Q_{10} of 2.2.
	DT_{50lab} (20°C, anaerobic): ‡ Anaerobic data not required for intended use. Non-standard anaerobic water sediment study showed DT50 (first order) as 146 days
	degradation in the saturated zone: ‡ not submitted, not required.
Field studies ‡ (state location, range or median with n value)	DT_{50f} (Parent): ‡ Northern Europe: 16-119 days (n=6) Southern Europe: 77-97 days (n=2) For FOCUSgw modelling for parent - Used geometric mean from all studies 39.1 days normalised to 20°C (56% transformed to M48 with 44% transformed to other compounds).

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

	DT_{90f} (Parent): ‡ Northern Europe 54-395 days (n=6) Southern Europe 256-323 days (n=2)
Soil accumulation and plateau concentration ‡	Fluoxastrobin could accumulate if used year on year. Plateau concentration after three years worth of applications is calculated as 0.032 mg/kg assuming a DT50 of 119 days and a total annual application of 97.5 g/ha (seed treatment plus 2 foliar treatments with crop interceptions of 50% and 70% respectively)

Soil adsorption/desorption (Annex IIA, point 7.1.2)

K_f /K_{oc} ‡ K_d ‡ pH dependence ‡ (yes / no) (if yes type of dependence)	K_{oc} parent 424-1582 (mean 848, 1/n=0.84-0.87 mean 0.86, n=4) M48 14-181.5 (mean 60.25, 1/n = 0.92-0.98, mean 0.95 n =4) M40 37-87 (mean 59, 1/n = 0.86-0.95, mean 0.9, n = 4) M48 adsorption appeared to decrease with increasing soil pH. No evidence that parent or M40 adsorption influenced by soil pH. 2-chlorophenol: no data available, **data required**. For FOCUSgw modelling- Mean values used. For M48 and high pH soils, K_{oc} 14, 1/n = 0.94 is appropriate.

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

Column leaching ‡	No data submitted, not required as satisfactory batch sorption data are available.
Aged residues leaching ‡	No data submitted, batch adsorption and modelling used to address this area.
Lysimeter/ field leaching studie ‡	No data submitted, batch adsorption and modelling used to address this area.

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

PEC (soil) (Annex IIIA, point 9.1.3)

Parent

Method of calculation	**Parent** DT50: 119 days Kinetics: 1st order Field or lab: Representative worst case from field studies and accumulated soil residue from previous years. **M48** Field or lab: Representative worst case from field studies when formed at 6.3% of total dose 89-258 days after application. **2-chlorophenol** Based on worst case maximum formation estimate of 49.2 %.
Application rate	Crop: Cereals Seed treatment : pre-emergence therefore no crop interception Foliar treatment: 1st at 50% crop interception and 2nd at 70% crop interception Number of applications = 1 seed treatment plus 2 foliar Interval 182 days between seed treatment and 1st foliar and 14 days between the 2 foliar treatments. Application rate: 17.25 g/ha (seed treatment) plus 2 x 200 g/ha (foliar treatment)

$PEC_{(s)}$ (mg/kg)		Multiple application Parent Actual	Multiple application Time weighted average	Multiple application Actual
		Parent	Parent	Metabolite M48
Initial		0.242	0.242	--
Short term	24h	0.241	0.242	--
	2d	0.240	0.241	--
	4d	0.237	0.240	--
Long term	7d	0.233	0.238	--
	89d	0.206	0.224	0.0149
	100d	0.135	0.184	--
	258d	0.054	0.125	0.0149

PEC (s) (maximum) **2-chlrophenol**: 0.033mg/kg

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

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)	pH 4: Stable to hydrolysis pH 7: Stable to hydrolysis pH 9: Stable to hydrolysis
Photolytic degradation of active substance and relevant metabolites ‡	Artificial radiation was equated to summer days in Athens (Greece, 38°N): fluoxastrobin DT50s: 33 days (ring 1) and 30 days (ring 3). Under sterile conditions M36 formed at 23.6% (ring 1) and 17.1% (ring 3) after 8 days continuous experimental irradiation. In a microbially active aqueous photolysis laboratory study with sediment present M36 was not detectable.
Readily biodegradable (yes/no)	No data submitted, therefore not readily biodegradable.
Degradation in water/sediment - DT_{50} water ‡ - DT_{90} water ‡	26-42 days 85-140 days (1st order, r2 = 0.97-0.98, n=2) Modelled water degradation (excludes dissipation through partitioning to sediment).
- DT_{50} whole system ‡	144-182 days
- DT_{90} whole system ‡	477-603 days (1st order, r2=0.94, n=2)
Mineralization	1.4-2.4% AR after 101 days (n=2)
Non-extractable residues	10.7-11.0% AR (at 101 days, n=2)
Distribution in water / sediment systems (active substance) ‡	Maximum of 60.4-73.3% AR in sediment after 14 days (n=2).
Distribution in water / sediment systems (metabolites) ‡	M48 2.6-15.9% AR in water after 122 days (n=2) 2-chlorophenol: concomitant to M48, amounts above 10 % cannot be precluded.

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

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

Parent and metabolite M48

Method of calculation	**Parent** Water degradation DT50 42 days (normalised for N and S Europe using representative temperature profiles) Kinetics: first order. Representative worst case from laboratory water sediment studies. Adsorption and desorption to sediment was modelled based on data from the soil adsorption study (mean Koc 848ml/g, 1/n =0.86) **M48** Max total dose (400g/ha) rate assumed, with 2.38% spray drift of parent into water used. Peak M48 seen in laboratory water sediment studies used to predict amount of M48 formed from parent with factor used to correct for molecular weight difference.
Application rate	Crop: cereals Number of application: 2 foliar application applications of 200g/ha with 14 day application interval. Water body assumptions: volume of $30m^3$, with 5 cm of sediment having a bulk density of 0.8 g/cm^3 and an oc% of 5%. Worst case assumption that no incoming water from upstream.
Main routes of entry	Drift rate of 2.77% at 1m used even though calculations assumed 2 applications [This is more worst case than the agreed EU rules where 1x2.77% would apply, (2x2.38% gives a lower calculated concentration than 1x 2.77%)]. Drift rate of 0.2% at 15m again calculations assumed 2 applications. **Note: PECsw from drainflow route of entry are presented in the DAR based on the UK (PSD) scheme.** **No PECsw from run off route of entry are calculated.**

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

PEC$_{(sw)}$ (µg/l)		Northern Europe 2 x Foliar applications (1m buffer) Actual	Northern Europe 2 x Foliar applications (1m buffer) Time weighted average	Southern Europe 2 x Foliar applications (1m buffer) Actual	Southern Europe 2 x Foliar applications (1m buffer) Time weighted average	2 x Foliar applications M48
Initial		2.12	2.12	2.11	2.11	0.38
Short term	24h	1.71	1.91	1.71	1.91	
	2d	1.32	1.71	1.31	1.71	
	4d	0.54	1.32	0.53	1.31	
Long term	7d	0.54	1.03	0.53	1.02	
	14d	0.53	0.80	0.52	0.79	
	21d	0.52	0.71	0.51	0.70	
	28d	0.52	0.67	0.50	0.66	
	42d	0.50	0.61	0.48	0.60	

PEC$_{(sw)}$ (µg/l)		Northern Europe 2 x Foliar applications (5m buffer) Actual	Northern Europe 2 x Foliar applications (5m buffer) Time weighted average	Southern Europe 2 x Foliar applications (5m buffer) Actual	Southern Europe 2 x Foliar applications (5m buffer) Time weighted average
Initial		0.44	0.44	0.43	0.43
Long term	14d	0.11	0.16	0.11	0.16

PEC$_{(sw)}$ (µg/l)		Northern Europe 2 x Foliar applications (15m buffer) Actual	Northern Europe 2 x Foliar applications (15m buffer) Time weighted average	Southern Europe 2 x Foliar applications (15m buffer) Actual	Southern Europe 2 x Foliar applications (15m buffer) Time weighted average
Initial		0.15	0.15	0.15	0.15
Long term	14d	0.04	0.06	0.04	0.06

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

PEC (sediment)

Parent

Method of calculation	Spray drift to surface water 2.38%. Even incorporation into 5 cm of sediment, sediment density of 1.3 g cm3 and no dissipation between applications was assumed. Maximum % fluoxastrobin seen in the sediment/water studies was 73.3% after 14 days dropping to 58.1% after 122 days.
Application rate	Cereals. 2 foliar applications at 200 g/ha. 14 day application interval into a 30 cm deep stationary water body.

PEC$_{(sed)}$ (µg/kg)	2 x foliar applications Parent Actual
Initial	
Short term	Peak of 10.7 after 14 days
Long term	Study end (122 days): 7.6

Assuming no dissipation between foliar applications (2 x 200 g/ha), 2.38% drift at 1m to a 30 m deep static water body the pseudo PECsw for use in the sediment dweller risk assessment is 3.17 µg /l.

PEC (groundwater) (Annex IIIA, point 9.2.1)

Method of calculation and type of study (*e.g.* modelling, monitoring, lysimeter)	Modelling using FOCUS PELMO 1.1.1. Cereals all scenarios.
Application rate	Cereals: autumn application of 17.5 g/ha (Sept/Oct depending on scenario) with 2 foliar applications in Spring each of 200 g/ha (March/April). 0% interception for the seed treatment and interception rates of 50% and 70% for the first and second foliar treatments respectively. Assumed 3 treatments to cereals every year.

PEC$_{(gw)}$

Maximum concentration	--
Average annual concentration (Results quoted for modelling with FOCUSgw scenarios, according to FOCUS guidance)	FOCUS defined 80th percentile 1m annual average concentrations for the proposed use on cereals: parent: <0.001 µg/l. M48: 0.002-3.65 µg/l.

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

PEC(gw) - FOCUS modelling results

	Scenario	PELMO 1.1.1 Parent [DT_{50} 39 days, Koc 848ml/g, 1/n 0.86] (µg/l)	Metabolite (µg/l)	
			PELMO 1.1.1 M48 [DT_{50} 54 days, Koc 60ml/g, 1/n 0.95]	PELMO 3.3.2 M48 [DT_{50} 54 days, Koc 14ml/g, 1/n 0.94] pertinent for high pH soils
PELMO /winter cereals	Chateaudun	<0.001	0.260	2.46
	Hamburg	<0.001	0.986	N/A (scenario top soil pH 6.4)
	Jokioinen	<0.001	0.510	N/A (scenario top soil pH 6.2)
	Kremsmunster	<0.001	0.629	3.65
	Okehampton	<0.001	0.936	N/A (scenario top soil pH 5.8)
	Piacenza	<0.001	1.033	3.0
	Porto	<0.001	0.036	N/A (scenario top soil pH 4.9)
	Sevilla	<0.001	0.002	0.58
	Thiva	<0.001	0.106	1.2

NOTE: No groundwater assessment for metabolite 2-chlorophenol provided. Data gap.

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

Direct photolysis in air ‡	Not submitted.
Quantum yield of direct phototransformation	Mean quantum yield of 0.00098 (E isomer).
Photochemical oxidative degradation in air ‡	DT50 of 9.9 hours in air derived by the Atkinson method of calculation assuming a global 12 hour concentration of OH radicals of 1.5 x 10^6 radicals per cm^{3}..
Volatilization ‡	from plant surfaces: ‡ Not submitted, not required. from soil: ‡ Not submitted, not required.

PEC (air)

Method of calculation	--

$PEC_{(a)}$

Maximum concentration	Negligible due to low vapour pressure and calculated DT50.

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

Definition of the Residue (Annex IIA, point 7.3)

Relevant to the environment	**Soil** Definitions for risk assessment: fluoxastrobin, Z-isomer of fluoxastrobin, M48-E, 2-chlorophenol, M40 (anaerobic metabolite). Definitions for monitoring: fluoxastrobin, Z-isomer of fluoxastrobin, 2-chlorophenol (assessment needs to be finalized). **Water** **Groundwater** Definitions for risk assessment: fluoxastrobin, Z-isomer of fluoxastrobin, M48-E, 2-chlorophenol, Definitions for monitoring: fluoxastrobin, 2-chlorophenol (assessment needs to be finalized). **Surface water** Definitions for risk assessment: fluoxastrobin, Z-isomer of fluoxastrobin, M48-E, 2-chlorophenol, M-40 (anaerobic metabolite). Definitions for monitoring: fluoxastrobin, Z-isomer of fluoxastrobin, 2-chlorophenol (assessment needs to be finalized). **Air** Definitions for risk assessment: fluoxastrobin Definitions for monitoring: fluoxastrobin

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

Soil (indicate location and type of study)	New substance. Not available, not required.
Surface water (indicate location and type of study)	New substance. Not available, not required.
Groundwater (indicate location and type of study)	New substance. Not available, not required.
Air (indicate location and type of study)	New substance. Not available, not required.

Classification and proposed labelling (Annex IIA, point 10)

with regard to fate and behaviour data	Possible candidate for R53

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

Appendix 1.6: Effects on non-target Species

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

Acute toxicity to mammals ‡	Rat LD50 (oral) > 2000 mg a.s. /kg bw
Acute toxicity to birds ‡	Rat NOEC 10,000 ppm a.s. in diet (742-764 mg a.s. /kg bw /day)
Dietary toxicity to birds ‡	*Colinus virginianus* (Bobwhite quail): LD50 (oral) > 2000 mg a.s. / kg bw, NOEL 2000 mg a.s. / kg bw
Reproductive toxicity to birds ‡	*Colinus virginianus* (Bobwhite quail): 5 day LC50 (oral) > 5000 ppm a.s. in diet (966 mg a.s. /kg bw /day), NOEC 625 ppm a.s. in diet (151 mg a.s. /kg bw /day). *Anas platyrhynchos* (Mallard duck): 5 day LC50 (oral) > 5000 ppm a.s. in diet (2194 mg a.s. /kg bw /day), NOEC 625 mg a.s. in diet (285 mg a.s. /kg bw /day).
Reproductive toxicity to birds	*Colinus virginianus (Bobwhite quail).:* *NOEC 1000 ppm a.s. in diet (74 mg a.s. / kg bw / day)* *Anas platyrhynchos (Mallard duck):* *NOEC 461 ppm a.s. in diet (51 mg a.s. / kg bw / day)*

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

Application rate (kg as/ha)	Crop	Category (*e.g.* insectivorous bird)	Time-scale	TER	Annex VI Trigger
400g a.s./ha (total dose)	Cereals (foliar application x2)	Large (>100g) herbivorous bird	Acute	> 186	10
400g a.s./ha (total dose)	Cereals (foliar application x2)	Large (>100g) herbivorous bird	Short-term	> 112	10
400g a.s./ha (total dose)	Cereals (foliar application x2)	Small (<100g) insectivorous bird	Acute	> 485	10
400g a.s./ha (total dose)	Cereals (foliar application x2)	Small (<100g) insectivorous bird	Short-term	> 862	10
400g a.s./ha (total dose)	Cereals (foliar application x2)	Large (>100g) herbivorous bird	Long-term	10.3	5

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

Application rate (kg as/ha)	Crop	Category (*e.g.* insectivorous bird)	Time-scale	TER	Annex VI Trigger
400g a.s./ha (total dose)	Cereals (foliar application x2)	Small (<100g) insectivorous bird	Long-term	79.5	5
400g a.s./ha (total dose)	Cereals (foliar application x2)	Small (<100g) herbivorous mammal	Acute	> 62	10
400g a.s./ha (total dose)	Cereals (foliar application x2)	Small (>100g) herbivorous mammal	Long-term	223	5
400g a.s./ha (total dose)	Cereals (foliar application x2)	Small (<100g) insectivorous mammal	Acute	> 5141	10
400g a.s./ha (total dose)	Cereals (foliar application x2)	Small (<100g) insectivorous mammal	Long-term	18519	5

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

Group	Test substance	Time-scale	Endpoint	Toxicity (mg/l)
Laboratory tests ‡				
Oncorhychus mykiss (Rainbow trout)	Technical fluoxastrobin	Acute	96h LC50	0.435 mg a.s./L
Daphnia magna (water flea)	Technical fluoxastrobin	Acute	48h EC50 (immobilisation)	0.48 mg a.s./L
Americamysis bahia (saltwater mysid)	Technical fluoxastrobin	Acute	96h LC50	0.0604 mg a.s./L
Gammarus pulex	Technical fluoxastrobin	Acute	48h EC50 (immobilisation)	0.15 mg a.s./L
Pseudo-kirchneriella subcapitata (alga)	Technical fluoxastrobin	Acute	72h EbC50 (cell density)	0.35 mg a.s./L
Lemna gibba	Technical fluoxastrobin	Acute	7 day ErC50 (growth rate)	> 6.0 mg a.s./L
Oncorhychus mykiss (ELS)	Technical fluoxastrobin	Long-term	95 day NOEC	0.0286 mg a.s./L
Daphnia magna	Technical fluoxastrobin	Long-term	21 day NOEC	0.18 mg a.s./L
Americamysis bahia (saltwater mysid shrimp)	Technical fluoxastrobin	Long-term	28 day NOEC	0.00061 mg a.s./L

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

Group	Test substance	Time-scale	Endpoint	Toxicity (mg/l)
Chironomus riparius (sediment dwelling midge)	Technical fluoxastrobin	Long-term	28 day EC5 (development rate)	1.2 mg a.s./L
Oncorhychus mykiss (Rainbow trout)	HEC 5725-deschlorophenyl	Acute	96h LC50	> 102 mg metabolite /L
Daphnia magna	HEC 5725-deschlorophenyl	Acute	48h EC50 (immobilisation)	> 100 mg metabolite /L
Pseudo-kirchneriella subcapitata	HEC 5725-deschlorophenyl	Acute	72h EbC50 (cell density)	100 mg metabolite /L
Oncorhychus mykiss	HEC 5725-carboxylic acid	Acute	96h LC50	> 95.7 mg metabolite /L
Daphnia magna	HEC 5725-carboxylic acid	Acute	48h EC50 (immobilisation)	> 100 mg metabolite /L
Pseudo-kirchneriella subcapitata	HEC 5725-carboxylic acid	Acute	72h EbC50 (cell density)	115 mg metabolite /L
Chironomus riparius	HEC 5725-carboxylic acid	Long-term	28 day EC5 (emergence)	28.4 mg metabolite/L
Oncorhychus mykiss	HEC 5725 EC100	Acute	96h LC50	3.29 mg product/L
Daphnia magna	HEC 5725 EC100	Acute	48h EC50 (immobilisation)	5.0 mg product/L
Pseudo-kirchneriella subcapitata	HEC 5725 EC100	Acute	72h EbC50 (cell density)	4.8 mg product/L
Gammarus pulex (water sediment single species laboratory study)	HEC 5725 EC100	Long-term	28 day NOEC	0.0316 mg a.s./L

Microcosm or mesocosm tests

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

Note: In view of the lower aquatic toxicity of metabolites compared with that for fluoxastrobin and that these metabolites will be present at lower concentrations, the aquatic risk assessment is covered by the active substance and no metabolite TERs have been calculated.

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

TERs from exposure to active substance (fluoxastrobin) – from spray drift contamination at 1 metre (overall 90th percentile) and also at 5-15 metres for the most sensitive tested aquatic species:

Application rate (kg as/ha)	Crop	Organism	Time-scale	Distance (m)	TER	Annex VI Trigger
400g a.s./ha (total dose)	Cereals (foliar application x2)	*Oncorhychus mykiss*	Acute	1 metre	205	100
400g a.s./ha (total dose)	Cereals (foliar application x2)	*Daphnia magna*	Acute	1 metre	226	100
400g a.s./ha (total dose)	Cereals (foliar application x2)	*Americamysis bahia*	Acute	1 metre	28	10-100*
400g a.s./ha (total dose)	Cereals (foliar application x2)	*Gammarus pulex*	Acute	1 metre	71	10-100*
400g a.s./ha (total dose)	Cereals (foliar application x2)	*Pseudo-kirchneriella subcapitata*	Acute	1 metre	142	10
400g a.s./ha (total dose)	Cereals (foliar application x2)	*Lemna gibba*	Acute	1 metre	2830	10
400g a.s./ha (total dose)	Cereals (foliar application x2)	*Oncorhychus mykiss*	Long-term	1 metre	13	10
400g a.s./ha (total dose)	Cereals (foliar application x2)	*Daphnia magna*	Long-term	1 metre	85	10
400g a.s./ha (total dose)	Cereals (foliar application x2)	*Americamysis bahia*	Long-term	1 metre 5 metres 15 metres	**0.76**[#] **3.8**[#] 10.2[#]	10
400g a.s./ha (total dose)	Cereals (foliar application x2)	*Gammarus pulex*	Long-term	1 metre 5 metres	14.9 71.8	10
400g a.s./ha (total dose)	Cereals (foliar application x2)	*Chironomus riparius*	Long-term	1 metre	379	10

* Annex VI trigger can be reduced from 100 up to 10 due to the numbers of tested invertebrate species (8) permitting a reduction in the uncertainty factor applying to the lowest toxicity values (as per HARAP 1999 and SANCO 2002 aquatic ecotoxicology guidance).
[#] Toxicity endpoint compared with 14 day t.w.a. PEC (other values based on comparison with initial PEC).

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

TERs from exposure to formulation (HEC 5725 EC100) - spray drift contamination at 1 metre (overall 90th percentile):

Application rate (kg product /ha)	Crop	Organism	Time-scale	Distance (m)	TER	Annex VI Trigger
4 litres /ha (total dose)	Cereals (foliar application x2)	*Oncorhychus mykiss*	Acute	1 metre	178	100
4 litres /ha (total dose)	Cereals (foliar application x2)	*Daphnia magna*	Acute	1 metre	270	100
4 litres /ha (total dose)	Cereals (foliar application x2)	*Pseudo-kirchneriella subcapitata*	Acute	1 metre	259	10

TER from exposure to fluoxastrobin via drainflow contamination for the aquatic organism with the most sensitive toxicity endpoint:

Application rate (kg as/ha)	Crop	Organism	Time-scale	TER	Annex VI Trigger
400g a.s./ha (total dose)	Cereals (foliar application x2)	*Americamysis bahia* (saltwater mysid shrimp)	Long-term	7.6	10

Note: Above drainflow TER estimate uses the maximum (initial) drainflow PEC. Given that treatment related mortality effects were not evident in the 28-day chronic toxicity study until day 16, it is considered more appropriate to compare the mortality NOEC from this study with the 14 day twa drainflow PEC of 0.00001 mg a.s./l (from Section B.8.5.1.2). Using this latter value, the refined drainflow mysid shrimp TER in relation to long-term mortality effects is 61.

Bioconcentration

Bioconcentration factor (BCF) ‡	52.1
Annex VI Trigger:for the bioconcentration factor	100
Clearance time (CT_{50}) (CT_{90})	0.41-0.45 days (whole fish) Not calculated
Level of residues (%) in organisms after the 14 day depuration phase	95-96% depuration after 14 days

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

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

Acute oral toxicity ‡	48h LD50 (technical fluoxastrobin): > 843 µg a.s./bee 48h LD50 (HEC 5725 EC100): 255 µg product /bee (equal to 25.5 µg a.s./bee) 96h LD50 (HEC 5725 EC100): 144 µg product /bee (equal to 14.4 µg a.s./bee)
Acute contact toxicity ‡	48h LD50 (technical fluoxastrobin): > 200 µg a.s./bee 48h LD50 (HEC 5725 EC100): 297 µg product /bee (equal to 29.7 µg a.s./bee)

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

Application rate (kg as/ha)	Crop	Route	Hazard quotient	Annex VI Trigger
Laboratory tests				
200g a.s./ha	Cereals	Oral (48h)	<0.24 (active)	50
		Oral (48h)	8.7 (product)	50
		Oral (96h)	15.4 (product)	50
		Contact (48h)	<1.0 (active)	50
		Contact (48h)	7.5 (product)	50

Field or semi-field tests N/A

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

Species	Stage exposed	Test Substance	Dose (kg as/ha)	Endpoint	Effect (compared with untreated)	Trigger value
Laboratory tests						
Aphidius rhopalosiphi (aphid parasitoid)	Adult	HEC 5725 EC100(glass plate substrate)	80g a.s./ha	Corrected mortality (2DAT)	58% LR50 68.1g a.s./ha	50%
Aphidius rhopalosiphi (aphid parasitoid)	Adult	HEC 5725 EC100 (leaf substrate)	200g a.s./ha	Corrected mortality (2DAT)	82% LR50 34.1g a.s./ha	50%

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

Species	Stage exposed	Test Substance	Dose (kg as/ha)	Endpoint	Effect (compared with untreated)	Trigger value
Typhlodromus pyri (predatory mite)	Proto-nymph	HEC 5725 EC100(glass plate substrate)	200g a.s./ha	Corrected mortality (7DAT)	77% (sig. P=<0.025) LR50 = 122.2g a.s./ha	50%
Typhlodromus pyri (predatory mite)	Proto-nymph	HEC 5725 EC100 (leaf substrate)	200g & 400g a.s./ha	Corrected mortality (7DAT) Eggs laid / female (8-14DAT)	0% & 25% (latter sig. P=0.004) 6% reduction & 20% increase (both N/S) LR50 > 400g a.s./ha	50%
Aloechara bilineata (rove beetle)	Adult	HEC 5725 EC100 (soil substrate)	200 & 400 g a.s./ha	Reproduc-tion (no. of F1 adults)	3% & 15% reduction (Sig at 2N) (no mortality effects)	50%
Poecilus cupreus (carabid beetle)	Adult	HEC 5725 EC100, (soil substrate)	200 & 400 g a.s./ha	Mortality & food consump-tion (up to 14 DAT)	No mortality No difference in food consumption	50%
Coccinella septem-punctata (ladybird)	Larvae	HEC 5725 EC100 (glass plate substrate)	35g a.s./ha	Corrected mortality (17DAT)	59% (sig. P<0.05) LR50 12.4g a.s./ha	50%
Coccinella septem-punctata (ladybird)	Larvae	HEC 5725 EC100 (leaf substrate)	200g a.s./ha	Corrected mortality (17DAT)	75% (sig. P<0.05) LR50 71.7g a.s./ha	50%
Chryso-perla carnea (lacewing)	Larvae	HEC 5725 EC100 (glass plate substrate)	200 & 400 g a.s./ha	Corrected mortality Eggs laid / female F1 egg fertility	52% & 26% (Sig. P<0.05) 10% & 7.7% reduction (N/S) 5.9 & 3.75 increase (N/S) LR50> 500g a.s./ha	50%

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

In a semi-field trial using potted wheat plants effects of exposure to 'HEC 5725 EC100' treated leaves on the reproductive capacity of *Aphidius rhopalosiphi* were examined by counting the numbers of subsequently parasitised (mummified) aphids per exposed female (aphids being introduced 24 hours after exposure). 'HEC 5725 EC100' was applied twice with a 14 day spray interval at the recommended individual dose of 200g a.s./ha. Reproductive capacity was reduced by 32% following exposure to freshly sprayed dried deposits but by only 13% following exposure to aged deposits (14DAT2).

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

Acute toxicity ‡	LC50 for fluoxastrobin, HEC 5725-des-chlorophenyl (M48), & HEC 5725-carboxylic acid (M40): All >500 mg a.s. or 1000 mg metabolite /kg dry soil #
Reproductive toxicity ‡	NOEL fluoxastrobin: =1000g a.s./ha (≡1.33 mg a.s./kg dry soil) NOEL HEC 5725-des-chlorophenyl: =1000 mg metabolite/ kg dry soil #

Includes EPPO correction factor for the active substance of 2 - due to high organic matter content of test soil and log Kow of > 2 (to allow for possible increased adsorption of active / metabolite in test soil). The log Kow of the metabolites is < 2 and therefore no correction factor required for these.

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

Application rate (kg as/ha)	Crop	Time-scale	TER	Annex VI Trigger
400g a.s./ha	Cereals	Acute	>2066	10
400g a.s./ha	Cereals	Long-term	= 5.5	5

Above relates to the active substance fluoxastrobin. For the soil metabolite HEC 5725-des-chlorophenyl (M48), the acute and chronic TERs are $\geq$ 67114.

Effects on other soil macro-organisms that contribute to organic matter breakdown (IIIA 10.6.2)

Species & study type	Test substance	Ecological endpoint	Soil PEC #	TER
Folsomia candida: 28 day chronic study	Technical fluoxastrobin	NOEC: 5 mg a.s. / kg dry soil *	0.242	21
Folsomia candida: 28 day chronic study	HEC 5725-deschlorophenyl	NOEC: 100 mg metabolite / kg dry soil	0.0149	6711
Hypoaspis aculeifer: 21 day chronic study	Bayer UK 831 (100g fluoxastrobin / litre)	NOEC: 10 mg a.s. /kg dry soil	0.242	41

* Includes EPPO correction factor of 2 due to high organic matter content of test soil and log Kow of > 2
\# Combined initial soil PEC following seed treatment with 'Bayer UKA 148' and the maximum proposed spray dose of 'Bayer UK 831' – for details see Section B.8.3.

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

Note: Current EC terrestrial ecotoxicology guidance includes TER trigger of 5 for collembola / mites, values of less than this indicating need for a litter bag study (SANCO 2002)

Results of litter bag study: Litter degradation in soil was not inhibited from seed treatment with 'HEC 5725 FS050' followed by spray treatment with 'HEC 5725 EC100' (% straw degradation in both treated and untreated plots was 90% 154DAT) at a measured concentration (soil samples taken 6 days after spray application) of 0.121 mg a.s./kg dry soil – equivalent to 50% of the estimated maximum (initial) soil PEC of 0.242 mg a.s./kg dry soil.

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

Nitrogen mineralization ‡	Technical fluoxastrobin & HEC 5725-des-chlorophenyl (M48) & HEC 5725-carboxylic acid (M40): Use at up to 2.83 mg fluoxastrobin / kg dry soil or of 2.73 mg HEC 5725-des-chlorophenyl / kg dry soil or of 1.27 mg HEC 5725-carboxylic acid / kg dry soil had no statistically significant effects (effects < 25%) on nitrogen mineralization when assessed 28 DAT
Carbon mineralization ‡	Technical fluoxastrobin & HEC 5725-des-chlorophenyl (M48): Use at up to 2.83 mg fluoxastrobin / kg dry soil or of 2.73 mg HEC 5725-des-chlorophenyl / kg dry soil had no statistically significant effects (effects < 25%) on carbon mineralization when assessed 28 DAT

Note: Maximum soil PEC from proposed use (seed treatment plus foliar applications) = 0.242mg a.s. /kg dry soil.

Classification and proposed labelling (Annex IIA, point 10)

With regard to ecotoxicological data	N;	Dangerous for the environment;
	R50:	Very toxic to aquatic organisms;
	R53:	May cause long term adverse effects in the aquatic environment;
	S60:	This material and its container must be disposed of as hazardous waste;
	S61:	Avoid release to the environment. Refer to special instructions / Safety data sheet

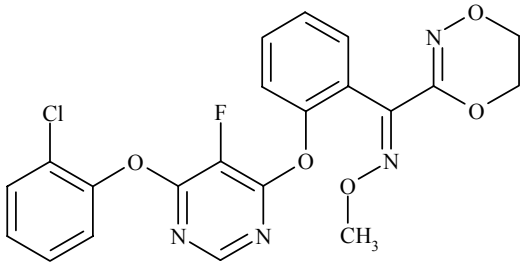
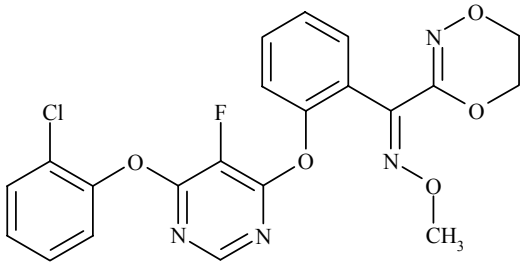
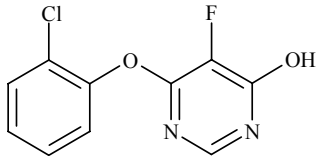
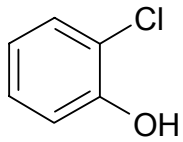
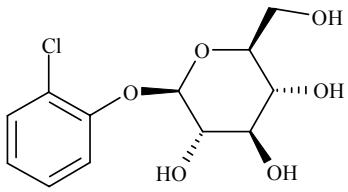
‡ Endpoints identified by EU-Commission as relevant for Member States when applying the Uniform Principles

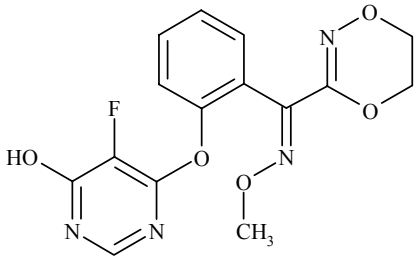
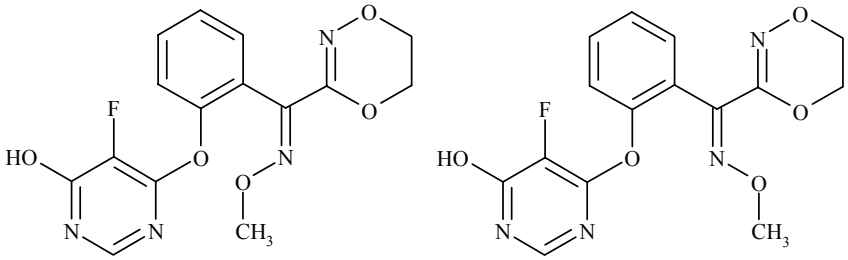
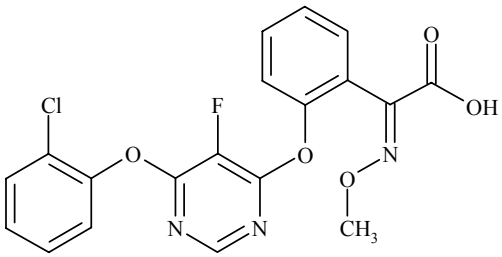
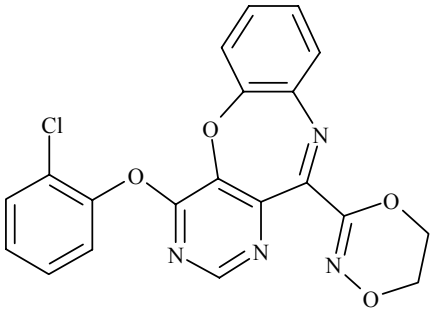
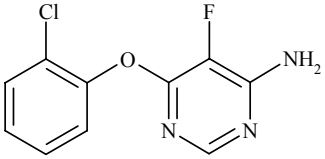
APPENDIX 2 – ABBREVIATIONS USED IN THE LIST OF ENDPOINTS

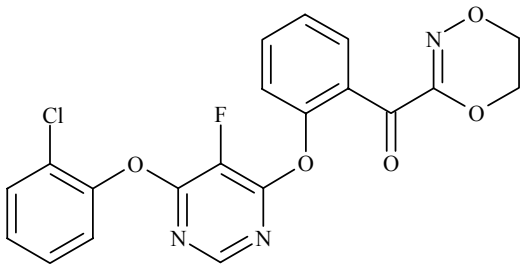
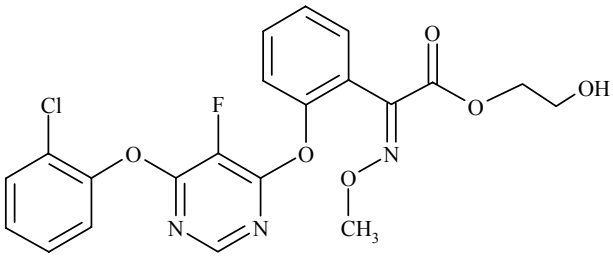
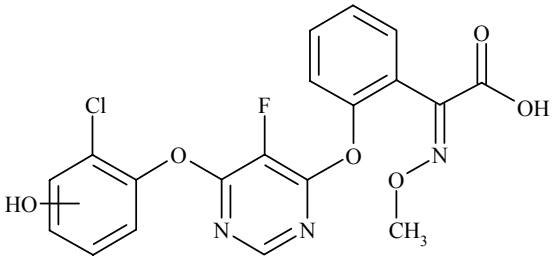
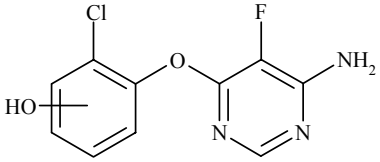
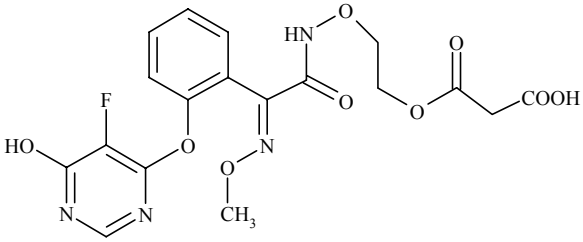
ADI	acceptable daily intake
AOEL	acceptable operator exposure level
ARfD	acute reference dose
a.s.	active substance
bw	body weight
CA	Chemical Abstract
CAS	Chemical Abstract Service
CIPAC	Collaborative International Pesticide Analytical Council Limited
d	day
DAR	draft assessment report
DM	dry matter
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
ε	decadic molar extinction coefficient
EC_{50}	effective concentration
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINKS	European List of New Chemical Substances
EMDI	estimated maximum daily intake
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 groundwater
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 – COMPOUND CODES USED IN THE CONCLUSION OR THE LIST OF ENDPOINTS

Code/Trivial name	Chemical name Structural formula
Compounds that appear in the conclusion and / or the list of end points	
Fluoxastrobin	
Z isomer of fluoxastrobin	
M55 / HEC 5725-phenoxy-hydroxypyrimidine	
M82	2-chlorophenol 
M84 / HEC 5725-2-chlorophenol-glucoside	

M48-E / HEC5725-E-des-chlorophenyl	
M48 / HEC5725-des-chloropheny (E + *Z*)	It may refer to the mixture of isomers or to the fact that the actual isomer is not specified in the study. 
M40 / HEC5725-carboxylic acid	
M36 / HEC5725-oxazepine	
M56 / HEC5725-phenoxy-aminopyrimidine	

Compounds that only appear in the list of end points	
M34 / HEC 5725-ketone	
M39 / HEC5725-carboxylic acid glycol ester	
M41 / HEC 5725-hydroxy carboxylic acid	
M57 / HEC5725-OH-phenoxy-amino-PMD	
M70 / HEC5725-des-chlorophenyl-glycol-MA	

M72 / HEC5725-des-chlorophenyl-carboxylic acid