Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

Risk assessment of the fungicide Aviator Xpro EC 225 with the active substances bixafen and prothioconazole

Opinion of the Panel on Plant Protection Products of the Norwegian Scientific Committee for Food Safety

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Summary

Aviator Xpro EC 225 is a new fungicide for use in cereals, containing the new active substance bixafen and the already approved active substance prothioconazole. Prothioconazole was assessed by the Norwegian Scientific Committee for Food Safety in 2006, and is therefore not included in this report.

VKM was requested by the Norwegian Food Safety Authority to consider the possible health risk for operators related to the properties of bixafen used in Aviator Xpro EC 225; in particular to evaluate the relevance of the effects of bixafen on liver and coagulation parameters observed in rats and mice, thyroid tumours and reproductive effects observed in rats, and the establishment of NOAELs and reference values. VKM was also asked to evaluate the fate and behaviour of bixafen in the environment, and the ecotoxicological effects and risks related to its use. The risk assessment was finalized in a meeting on May 24. 2013 by VKM's Scientific Panel on Plant Protection Products.

VKM's conclusions are as follows:

Health

VKM concluded that the liver effects reported in sub-chronic and chronic studies in rats, dogs and mice exposed to bixafen, as well as the effects on coagulating parameters, should be considered adverse and of relevance to humans.

It is the opinion of VKM that the thyroid follicular cell tumours reported in female rats exposed to bixafen is not sufficient to suggest that bixafen has a tumour inducing potential.

It is further the opinion of VKM that it cannot be excluded that the reduced pup weight during lactation in the two-generation study is mediated by bixafen via the milk, and that bixafen has a direct effect on the number of stillborn pups in the F1 and F2 generation.

Finally, the pup developmental variants and anomalies reported in the teratogenicity study are considered treatment related, and not as secondary effects related to maternal toxicity.

VKM proposes a NOAEL of 2.0 mg/kg bw/day based on a 2 year feeding study in rats.

VKM support/propose:

- ADI: 0.02 mg/kg bw/day
- AOEL: 0.13 mg/kg bw/day
- ARfD: 0.2 mg/kg bw/day

Risk calculations show minimal risk if personal protective equipment is used.

Environment

Bixafen is shown to be persistent in soil. VKM considers the results from a field study on a German site and the Finnish PEC calculator to be relevant and concludes that repeated annual applications can cause accumulation in soil under Norwegian conditions. There is also a potential for groundwater contamination from leaching of the metabolite M44.

VKM has concluded that the use of bixafen as an ingredient in Aviator Xpro EC 225 with the proposed application regime in Norway will represent a minimal risk for toxic effects to terrestrial organisms.

The toxicity of bixafen to aquatic organisms is high, and minimal risk of effects in surface waters can be achieved only if risk mitigation measures with bufferzones of 10 m are applied.

Background

VKM performs risk assessments in the context of pesticide registration cf. Regulation on Pesticides § 4. The Norwegian Food Safety Authority, National Registration Section, is responsible for reviewing and evaluating the documentation submitted by the pesticide notifier. The Norwegian Food Safety Authority takes the final regulatory action regarding registration or deregistration of pesticides based on VKMs risk assessment, along with a comparative assessment of risk and benefits, and the availability of alternatives (the principle of substitution).

The Norwegian Food Safety Authority submitted a request on April 18, 2013 for VKM to perform a risk assessment on use of the pesticide Aviator Xpro EC 225 containing the new active substance bixafen and the already approved active substance prothioconazole. The application is for use as a fungicide in cereals. Prothioconazole was assessed by the Norwegian Scientific Committee for Food Safety in 2006, and is therefore not included in this report. The risk assessment was finalized in June, 2013.

Terms of reference

Aviator Xpro EC 225 is a new product containing the active substance bixafen and the already approved active substance prothioconazole. The application is for use as a fungicide in cereals. Prothioconazole was assessed by the Norwegian Scientific Committee for Food Safety in 2006, and is therefore not included in this report.

In this regard, The Norwegian Food Safety Authority would like an assessment of the following:

- The human health risk for operators related to the properties of bixafen used in Aviator Xpro EC 225. The Panel is in particular asked to look at the following:
    - Evaluation of the effects of bixafen on the liver and the perturbation of the coagulation parameters observed at low doses, and if these should be considered as adverse effects.
    - Evaluation of the arguments put forward by the notifier stating that the perturbation of the coagulation parameters observed in studies on rat and mouse was due to vitamin K deficiency in the diet.
    - The relevance for humans of tumors observed in thyroid in the rat study.
    - Evaluation of the reproductive effects of bixafen observed in rats, especially fetus mortality and changes in pup body weight and organ weight during lactation.
    - Evaluation of the effects of bixafen observed in the teratogenicity study on rabbits.
    - The establishment of NOAELs and reference values (ADI, AOEL and ARfD).
- The fate and behaviour in the environment and the ecotoxicological effects and risks with regard to the properties of bixafen used in Aviator Xpro EC 225.

1 Background documentation

VKM's risk assessment is based on the Norwegian Food Safety Authority's evaluation of the documentation submitted by the applicant. The Norwegian Food Safety Authority publishes both their evaluation of Aviator Xpro EC 225 and their final regulatory action on the registration of the pesticide product at their homepage www.Mattilsynet.no.

2 Procedure

The first three steps of the risk assessment (hazard identification, hazard characterization and assessment of exposure) are performed by the Norwegian Food Safety Authority and involve an assessment of the documentation submitted by the pesticide notifier. The resulting report on hazard identification, hazard characterization and assessment of exposure, from which the summary is included in the present document, is then reviewed by VKM. This review may result in some amendments in the original documents of both the summary and the full report issued by the Norwegian Food Safety Authority (2011). The fourth step (risk characterization) is based on the three first steps and is VKM's conclusions or risk assessment.

2.1 HEALTH RISK ASSESSMENT

The assessment of health risk of pesticides is based on the adverse effects produced by the active substance and product in several experimental test systems including long term animal studies. On the basis of this, limits of exposure which represent no health risk are determined. The limits take account of the uncertainties of extrapolating data from animals to humans and are compared to the operator exposure and human exposure to possible residues in food.

The UKPoem and the German model are used to estimate operator exposure. The models are based on a limited number of studies and are not validated. Thus, the models may not always be sufficiently representative for Norwegian conditions. The limitations of model estimates of exposure are taken into consideration when the calculated level of exposure is close to the threshold limit for acceptable operator exposure (Acceptable Operator Exposure Level; AOEL). VKM uses the 75 percentile of exposure assessment for both UK poem and German model. VKM has to base the assessment on the models whenever exposure data for the product is missing.

VKM makes use of a higher safety factor when calculating AOEL and ADI in cases where the product contains critical active substances with serious adverse inherent properties (toxic to reproduction or carcinogenic).

In order to describe the exceeding of maximum tolerated dose, VKM makes use of a scale. The scale is based on the ratio between the estimated exposure based on models or measured exposure in field studies and the Acceptable Operator Exposure Level (AOEL). In cases where the estimated exposure significantly exceeds AOEL, the use of the products may lead to increased risk for health effects.

The following scale is used:

Very high excess of AOEL	more than 500% of the limit
High excess of AOEL	300 – 500% of the limit
Medium excess of AOEL	150-300% of the limit
Moderate excess of AOEL	100-150% of the limit

The limit is not exceeded

VKM may also consider co-formulants in the product when risk is to be determined. Consequently, if a product contains critical co-formulants it may be assessed to represent higher risk than what the inherent properties of active substances imply.

2.2 ENVIRONMENTAL RISK ASSESSMENT

The environmental risk assessment of pesticides involves predictions of exposure concentrations in various environmental compartments (e.g. soil and surface waters) that may occur after application of the pesticide. These predicted effect concentrations (PECs) are compared to exposure levels that are known to cause toxic effects to important groups of organisms representing the environmental compartments.

The environmental fate and possible ecotoxicological effects of pesticides are investigated in several laboratory- and field experiments. In environmental risk assessments of pesticides, Predicted Environmental Concentrations (PECs) are estimated by use of different scenarios for different parts of the environment (terrestrial, aquatic). The first parameter estimated is usually the initial concentration (PIEC, Predicted Initial Environmental Concentration), e.g. the concentration just after application (usually spraying). PIEC in soil is calculated assuming a homogenous distribution of areal dose in the upper 5 cm soil layer. For surface water, the PIEC is based on deposition of pesticides from spray drift in a standard size water body. The calculations are performed with application of buffer zones between the sprayed area and the water body.

The further exposure regime in different compartments is affected on the fate of the pesticide. The fate is dependent on processes such as photo degradation, hydrolysis, biodegradation and sorption to soil particles. These processes are studied in several standardised laboratory tests. In addition, field tests are used to study the dissipation of the pesticide in various agricultural soils. Based on the experimental fate studies, factors describing different fate processes may be derived and used in models that describe the fate of the pesticide in the soil as well as the transport to surface water and ground water. The concentrations of the pesticide in water are estimated by use of models with relevant scenarios based on EU's FOCUS-scenarios. The models produce maximum PEC and average PEC calculated for specified periods after pesticide application. In the surface water scenarios PEC is also calculated for the sediment phase.

Then the Toxicity Exposure Ratio (TER) is estimated for different groups of organisms. The TER is calculated as the ratio between the toxicity for the organism in question (expressed as LC50, EC50, NOEC etc., depending on organism and study type) and PEC or PIEC. Trigger values for TER, which express the acceptability of the risk for different organisms, have been defined by the EU. The risk is considered minimal when the TER does not exceed the trigger value.

In the terrestrial environment, the risk for toxic effects on bees and non-target arthropods is assessed according to other criteria. Hazard quotients for oral- (HQ_O) and contact toxicity (HQ_C) are estimated for bees. HQ_O and HQ_C are ratios between the standardized area dose of the product (g v.s. /ha) and acute toxicity for the bee (LD50, µg active ingredient/bee). Field experiments and expert evaluation is triggered whenever the hazard quotient is above 50.

For the non-target arthropods, the estimated hazard quotient (HQ) is the ratio between the area dose of the product (g active ingredient/ha), which is multiplied with a factor for multiple applications (MAF, multiple application factor) when appropriate, and the acute toxicity for the organism (LR50, g active ingredient/ha). According to EU, whenever the ratio value exceeds 2, further investigations are triggered.

VKM makes use of a scale in order to describe the risk of exposure for different organisms which live within and outside the spraying field. The scale is based on the ratio between the estimated exposure and the limit or the ratio between the TER and the TER trigger value designated each group of organism.

The following risk scale is used:

Very high risk	more than 500% of the limit
High risk	300 – 500% of the limit
Medium risk	150-300% of the limit
Moderate risk	110-150% of the limit
Minimal risk	the limit is not exceeded

The estimates of exposure concentrations are based on maximal concentrations, which exist during or shortly after spraying. The group of organism assessed (for example birds or leaf dwelling non-target organisms) is not always present during the period of maximal concentration. In the final risk assessment, VKM therefore takes into consideration whether, or to which extent, the organism in question actually will be exposed. This may cause that the risk is assessed lower than indicated by the scale above.

Additionally, uncertainties in the data base both with regard to establishments of limits and models of exposure concentrations are taken into consideration if relevant. This may also cause that the risk is assessed lower or higher than the risk scale. Any deviation from the risk scale is justified in this document.

3 Summary by the Norwegian Food Safety Authority (hazard identification, hazard characterization and assessment of exposure)

Aviator Xpro EC 225 is a new product containing two active substances bixafen and prothioconazole. Bixafen is a new active substance. The intended use is as fungicide in spring wheat, winter wheat, triticale, barley, rye and oats.

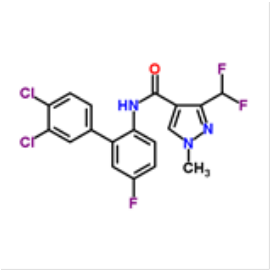
Aviator Xpro EC 225 has effect against several plant diseases caused by fungi or oomycetes. Aviator Xpro EC 225 is a mixture of two active substances with different mode of action. Both active ingredients have curative and preventive effects. They are systemic and can be quickly translocated within the plant. The standardized area dose is set to 1.25 L per hectare. Aviator Xpro 225 should be applied in a volume of 100 to 300 L/ha of water with a broadcast sprayer using ground directed spraying. Maximal recommended application number is 2 per season with 14-21 days in between.

The Norwegian Institute for Agricultural and Environmental Research recommend approval in spring wheat, winter wheat, triticale, barley, rye and oats.

3.1 IDENTITY AND PHYSICAL/CHEMICAL DATA

Product name:	Aviator Xpro EC 225
Active substances:	Bixafen and prothioconazole
Formulation:	Emulsion concentrate EC
Concentration of active substance:	Bixafen 75g/l, prothioconazole 150 g/l
IUPAC-name (bixafen):	N-(3′,4′-dichloro-5-fluorobiphenyl-2-yl)-3-(difluoromethyl)-1-methylpyrazole-4-carboxamide
CAS number (bixafen):	581809-46-3

Structural formula:



Molecular weight:	414.21 g/mol	
Water solubility:	Low	0.00049 g/l (20 °C)
Vapour pressure:	Low	4.6 x 10^{-8} Pa (20°C)
Henrys law const.:	Low	3.89 x 10^{-5} Pa m^3 mol^{-1}
log Pow:	High	3.3 (25 °C)
pKa:	-	

3.2 MAMMALIAN TOXICOLOGY

3.2.1 BIXAFEN

3.2.1.1 *Toxicokinetics*

Absorption: Bixafen was rapidly absorbed after oral administration. Based on the recoveries in bile, urine and carcasses, approximately 86% and 83% of the administered dose were absorbed by male and female rats, respectively. At low doses, the female rats AUC were approximately twice as high as those for males. Saturation of the absorption processes was noted at high doses.

Distribution: Maximum concentrations in the organs and tissues were observed between 1 and 8 hours after dosing. A rapid decline of the radioactivity concentrations in all organs and tissues was observed between 1 and 48 hours after administration. Residues levels in the organs and tissues were generally low with highest level in in the liver. There was no evidence of bioaccumulation in males or females.

Metabolism: Bixafen-desmethyl, formed by desmethylation of the pyrazole ring was the most predominant metabolite identified. Hydroxylation of bixafen and bixafen-desmethyl occurred at different positions, especially in the fluoro-phenyl ring. Hydroxy compounds were further conjugated with glucuronic acid. N-conjugation of bixafen-desmethyl with glucuronic acid was also found. Bixafen was also found to be conjugated with glutathione, and this was a major metabolic reaction in bile. Bixafen-desmethyl was also conjugated with glutathione. Cleavage occurs up to 4% of the administered dose.

Excretion: Approximately 93-99% of the administered dose had been eliminated in urine and faeces 72 hour after dosing. For all treatments, the urinary excretion was low (<3%) but female rats excreted approximately twice the amount of the administered radioactivity in urine than males. Biliary excretion was approximately 83% in males and 56% in females at 48 hours after dosing.

3.2.1.2 *Acute toxicity*

Acute toxicity of bixafen is low. No mortalities or clinical signs of toxicity were observed in the acute oral or dermal studies. Clinical signs of toxicity were observed at the maximum achievable concentration in the inhalation study and included bradypnoea, laboured breathing, piloerection, flaccid paralysis of hindlimbs and ungroomed coat. Gross necropsy revealed mild discolouration of the lungs.

3.2.1.3 *Genotoxicity*

A complete battery of *in vitro* and *in vivo* genotoxicity studies was conducted with bixafen. Based on these studies, bixafen is not genotoxic.

3.2.1.4 *Subchronic toxicity*

In the short-term studies on rats, a dose related increase in protrombine time, reduction in bilirubin levels, slight enzyme induction and increased liver weight were observed. Centrilobular hepatic hypertrophy and thyroid follicular cell hypertrophy was also dose

related. Increases in platelets, cholesterol and γ-glutamyl transferase activity were observed at the high dose level.

In the short-term studies on mice one female was found dead at the high dose level. This was related to haemorrhage. Dose related reduction in albumin and elevated ALAT and ASAT activities and liver effects were also observed. Focal/multifocal squamous cell hyperplasia in the stomach was observed at high dose level.

In the short-term studies in the dog, increased liver weight and enlarged centrilobular hepatocytes with vacuolated cytoplasm were observed. Haematological changes indicating anaemia were noted at the high dose level.

3.2.1.5 *Chronic toxicity and carcinogenicity*

In the initial 2-year chronic toxicity and carcinogenicity study, significant mortality and signs of haemorrhage were observed early in the study. The analysis of the diet showed levels of vitamin K < 0.3 mg/kg. The haemorrhagic syndrome was attributed to the lack of vitamin K in the diet. All males were therefore terminated without necropsy. The female rats remained in the study, but the diet was supplemented with 15.7 ppm vitamin K. At the high dose, two females died and this was attributed to haemorrhagic syndrome possibly caused by the low vitamin K3 content in the diet at the beginning of the study. Total bilirubin levels were reduced at all dose levels. A dose-related increase in cholesterol levels was also observed. Histopathological findings in the liver included centrilobular to panlobular hepatocellular hypertrophy and an increased incidence and/or severity of hepatocellular brown pigments and multinucleated hepatocytes. In the thyroid, there were increased incidences and/or severity of follicular cell hypertrophy, colloid alteration, brown pigments in follicular cells, follicular cell hyperplasia and an increase in the incidence of follicular cell tumours (adenoma & carcinoma incidences combined).

In the complementary male rat chronic toxicity and carcinogenicity study (supplemented with 8.2-10.6 ppm vitamin K), prothrombin times were significantly decreased. Dose-related reductions in total bilirubin were evident at all dose levels throughout the study. The cholesterol levels were also increased. The microscopic findings in the liver included increased incidences of centrilobular to panlobular hepatocellular hypertrophy, hepatocellular brown pigments, eosinophilic hepatocellular alterations and hepatic cystic degeneration. In the thyroid, there were increased incidences of follicular cell hypertrophy, colloid alteration, brown pigments in follicular cells and follicular cell hyperplasia. There was no evidence of any increase in the incidence of thyroid tumours.

In the carcinogenicity mice study, increased mortality in males occurred at the high dose level during the first twenty weeks of the study. The analysis of the diet showed levels of vitamin K < 0.3 mg/kg. The haemorrhagic syndrome was attributed to the lack of vitamin K in the diet. The diet was then supplemented with 15.7 ppm vitamin K. Several changes to the haematological parameters were observed. Microscopic findings in the liver included increased incidence of centrilobular hepatocellular hypertrophy and vacuolation in both sexes. In addition, male livers had increased incidences of hepatocellular brown pigments, single cell degeneration necrosis, multinucleated hepatocytes and mononuclear infiltrate. In the thyroid, there were increased incidences of follicular cell hyperplasia in both sexes. There was no evidence on any compound induced tumours in either sex.

In the chronic/carcinogenicity studies in rat and mice increased mortality was observed in males. This was attributed a haemorrhagic syndrome occurring early in the study period. The notifier analysed the diet and found levels of vitamin K < 0.3 mg/kg. The notifier conducted

studies where diet was supplemented with vitamin K. These studies showed that bixafen did not result in any significant changes to blood coagulation parameters (see 5.1.10 Mechanistic/supporting studies).The notifier then attributed the haemorrhagic syndrome observed in male rats and male mice in short-term and chronic studies to the lack of vitamin K in the diet.

The notifier argued further that the occurrence of haemorrhagic syndrome and the increased mortality in males, but not in the females, were due to a combination of vitamin K deficiency and enzyme induction seen in males. According to the notifer a literature search provided evidence for a synergistic effect of diets deficient in vitamin K and presence of liver enzyme induction, occurring preferentially in male rats, when exposed to a wide variety of chemical compounds that induce liver metabolising enzymes, when there is low vitamin K in the diet. The chemicals that cause this synergistic response have in common induction of cytochrome P450 2B enzymes. It is hypothesised that induction of CYP450 2B and/or CYP450 3A4 isoenzymes (i.e. those induced by PB) could result in reduction in one or more coagulation factors normally activated by the vitamin K cycle.

The EU rapporteur member state (RMS, UK) concluded that while some information is supportive of the argumentation of the notifier, it is possible that bixafen has some inherent ability to impair blood coagulation in animals on a diet containing normally adequate levels of vitamin K. The RMS supported this conclusion by the following:

- The quantitative data on vitamin K content of the diets are not available for most of the studies
- The supplementation level of 16 ppm vitamin K is in excess of the minimum recommended level for the vitamin K content of rodent diets (about 1 mg/kg in the diet)
- It is not clear what levels of vitamin K are appropriate for the testing and identification of a compound with anticoagulant or suspected anticoagulant properties in rodents
- The magnitude of enzyme induction is not particularly great.

EFSA has also concluded that the haemorrhagic effect observed at high doses in rats and mice does show that this is an intrinsic property of bixafen that may be masked by an excess of vitamin K in the diet.

3.2.1.6 *Reproductive toxicology and teratogenesis*

In the range finding one-generation rat study, there were treatment-related reductions on maternal body weight and body weight gain, some evidence of increased APTT times in males, increased liver and thyroid weights and reduced thymus weights. During lactation, pup weights were reduced (birth weight was not affected) and changes in organ weights were observed.

In the rat two-generation study, there were treatment-related reductions on maternal body weight and body weight gain, and parental organ weight changes (e.g. increased liver, kidney and spleen weight and reduced thymus weight). Hepatic hypertrophy (centrilobular and/or diffuse) was observed, this was associated with a decrease in vacuolisation. F1 and F2 pup weights were reduced during the lactation periods, and the reductions in F1 pups persisted into adulthood. It is unclear whether the organ weight changes observed in F2 pups were treatment related or secondary to reductions in pup weight. Since birth weight was unaffected by treatment and the reductions in pup weight was seen already from lactation day 4 (in the

range-finding study), this effect might be caused by either the presence of test material in the dam's milk, a change in the amount of milk produced by the dams or a change in the nutritional status of the milk. It cannot be excluded that the reduced pup weight during the lactation period is cause by the presence of the test material in the dam's milk.

The numbers of litters with stillborn pups were increased in the F1 and F2 generations when compared to concurrent controls, and were also slightly outside the historical control data for the laboratory. During the assessment in the EU this finding was regarded as inconsistent and insignificant, with minimal impact on overall numbers in the next generation, and the reproductive NOAEL was set at 2500 ppm. However, based on the increased number of stillborn at the highest dose level (2500 ppm), a NOAEL at 400 ppm should be considered.

It should be noted that the Purina diet used in both reproduction studies contained 1.3 ppm vitamin K (as menadione). There was some evidence of an effect on coagulation parameters in the range finding study, but coagulation parameters were not evaluated in the main multigenerational study.

In the rat developmental study, maternal body weight loss, reduced foetal weight and delayed skeletal development were observed. In the rabbit developmental study, the maternal effects included marked mortality (abortions/failure to maintain pregnancy and sacrificed for humane reasons), clinical signs, body weight loss and reductions in body weight gain, increased liver weight, liver (white foci and prominent lobulation) and urinary bladders findings (enlarged/purulent contents). The rabbit foetal findings included an increase in the number of runts, reduced foetal weight and visceral and skeletal findings. Adopting a precautionary approach, the increased percentage of litters with short innominate arteries and a dose related increase in the percentage of foetuses and litters with extra sternebral ossification site(s) at the mid and top dose levels are regarded as treatment related, because they are outside the historical control range.

3.2.1.7 *Neurotoxicity*

Not relevant.

3.2.1.8 *Mechanistic/supporting studies*

Male rats administered bixafen in diet (containing <0.3 ppm vitamin K3) exhibited a haemorrhagic syndrome (increased PT and APTT values) and a high rate of mortality. The addition of 16 ppm vitamin K to the diet significantly lowered these values after two weeks.

The test material induced slight increases in serum TSH. A slight reduction of T3 and T4 was also seen. There was an increase in BROD activity. A slight increase was also observed in mean UDPGT activity.

3.2.1.9 *Humane data*

No data reported.

3.2.1.10 *Reference values*

ADI: Based on the NOAEL of 2.0 mg/kg bw/day determined for male rats and an assessment factor of 100, an ADI of 0.02 mg/kg bw/day can be proposed for bixafen.

AOEL: Based on the NOAEL of 12.9 mg/kg bw/day determined for the 90-day rat study an assessment factor of 100, a short-term systemic AOEL of 0.13 mg/kg bw/day can be proposed for bixafen.

ARfD: Based on the NOAEL of 20.0 mg/kg bw/day determined for the rat development study an assessment factor of 100, an ARfD of 0.20 mg/kg bw/day can be proposed for bixafen.

3.2.1.11 *Metabolites*

Cereals is not a re-entry culture, therefore there is no risk of workers being exposed to plant metabolites. The exposure of crop inspectors to these metabolites is considered to be minimal, since the metabolites were found only in very low amounts in a 3N rotational crop study.

3.2.1.12 *Co-formulants*

One co-formulant is harmful if swallowed and its content in Aviator Xpro EC 225 is above the classification limit.

3.2.2 AVIATOR XPRO EC 225

3.2.2.1 *Acute toxicity*

The studies conducted with Aviator Xpro EC 225 showed low toxicity by the oral and dermal rout of exposure. The product was not found irritating to the skin, nor found to be a dermal sensitizer. However, the product was found to be irritating to the eyes, and should be classified as eye irritating in category 2 (H319: Causes serious eye irritation) according to the CLP criteria.

3.2.2.2 *Classification and labelling*

Aviator Xpro EC 225 should be classified as an eye irritant in category 2 (H319: Causes serious eye irritation), according to the CLP criteria.

3.2.2.3 *Dermal absorption*

No dermal absorption study has been conducted with the product Aviator Xpro EC 225. Therefore, EFSA's default values for dermal absorption (25% for the concentrated product and 75% for the spray dilution) have been used in the exposure calculations.

3.2.2.4 *Operator, worker and bystander exposure*

The AOEL for bixafen was exceeded in the UK Poem and in the German model without PPE (personal protective equipment). However, the estimated exposure was below the AOEL for bixafen when PPE was applied during mixing/loading and application. No re-entry activities are envisaged for the intended use, and the exposure estimates show no risk for bystanders. The combined level of exposure to the respective active substances (bixafen and prothioconazole) is acceptable for operators using field crop sprayers when personal protective equipment is worn.

3.2.3 RESIDUES IN FOOD OR FEED

The active substance prothioconazole and the product Proline EC 250 were evaluated by the Norwegian Scientific Committee for Food Safety in 2006.

Bixafen is a new active substance and Bayer CropScience AG has applied for approval in EU. The RMS (the United Kingdom) checked the completeness of the dossier and provided its initial evaluation of the dossier on bixafen in the Draft Assessment Report (DAR), which was received by the EFSA on 19 July 2011.

The European Commission (see Draft review report for the active substance bixafen finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 15 March 2013) supported the approval of the active substance bixafen. The EU concluded that it is appropriate to approve bixafen; however, it is necessary to include certain conditions and restrictions. Member States shall pay particular attention to the residues of bixafen and of its metabolites in rotational crops.

3.3 ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL EFFECTS

3.3.1 ENVIRONMENTAL FATE AND BEHAVIOUR

3.3.1.1 *Degradation in soil*

Bixafen is very persistent under standard aerobic laboratory conditions with up to 91 % unchanged bixafen left at the end of the study and with a half-life of > 1 year. The only metabolite identified was BYF 00587-desmethyl-pyrazole-4-carboxylic acid (M44) which ranged from 0.4 to 2.9 % of Applied Radioactivity (AR). Bound residues summed up to 11.2 % of AR within 120 days and CO2 to < 1.6 % of AR. The anaerobic degradation rate is low with DT50 > 1 year and no significant mineralization. Bound residue amounted to about 10 % AR. Photolysis cannot be regarded as an important route of degradation for bixafen in soil. Field dissipation studies indicate that the dissipation of bixafen is low in four Northern European soils, including a soil from a site in Sweden. The Hockey Stick model described the dissipation best, resulting in DT50s between 316 and 1235 days and a geometric mean of 537 days. For modelling the field DT50 SFO values were normalised to 197 - 340 days with a geometric mean of 249 days. A 6 year long soil accumulation study has been performed giving results that indicate a continued accumulation during the trial with no clear plateau being reached. The geometric mean DT50 of metabolite M44 was 25.4 days.

Aerobic degradation of the metabolite M44 has been investigated by using data from three of four soils in the degradation studies on bixafen. Half-lives were estimated to be between 11 and 55 days (geometric mean of 25.4 days).

3.3.1.2 *Sorption/mobility*

The sorption of bixafen in 5 different soils can be classified as very high with Kf: 41-103 (average 78) and Koc: 3477-4974 (average 3869). Average 1/n is 0,8766.

3.3.1.3 *Degradation in water*

Bixafen can be regarded as hydrolytically stabile. Photolysis is not an important degradation pathway for bixafen in water. According to the OECD criteria for ready biodegradability, Bixafen is not readily biodegradable. In a water/sediment study bixafen dissipated rather quickly from the water phase to the sediments with a half-life of about 25-27 days (SFO). The degradation for the whole system can be classified as low with DT50 > 1000 days (system values, SFO), geometric mean > 1000 days. DT90 > 1000 days.

3.3.1.4 *Fate in air*

Bixafen is not likely to volatilise significantly. A theoretical calculation of the potential for photo-oxidation of bixafen in the atmosphere has been submitted indicating a first order DT50 of 0.87 days. The 'long-term' half-life and chemical life time in the troposphere was estimated to be 1.31 days and 1.89 days, respectively.

3.3.2 ENVIRONMENTAL EXPOSURE

3.3.2.1 *Soil*

PECsoil, including PECplateau/accumulation has been estimated by Mattilsynet using the Finnish PEC calculator. PiEC (Predicted initial Environmental Concentration, immediately after the second application) was calculated to be 0.125 mg/kg and the maximum PEC (directly after application) after approximately 20 years of continuous use was 0.90 mg/kg when using worst case un-normalised field DT50. A clear plateau was not reached during the period the model runs.

3.3.2.2 *Groundwater:*

Bixafen is not likely to leach to groundwater at concentrations > 0.1 µg/L with the tested parameters. All nine EU scenarios gave 80th percentile PECgw values of <0,0001 µg/L even when using worst case input parameters in the modelling.

Metabolite M44 has been seen to leach to groundwater above the limit of 0.1 µg/L in all nine FOCUS scenarios. An application of 2x125 g bixafen/ha was used in the modelling but it is not believed that a somewhat lower application rate would change the conclusion of the groundwater assessment much.

3.3.2.3 *Surface water and sediment:*

Modelling with the EU surface water scenarios has been performed by the applicant and presented in the DAR, but this modelling was performed with a somewhat higher application rate (125 g a.s./ha) than what is relevant for Norway resulting in a worst case Step 3 PECsw of 0.800 µg a.s./L. Highest PECsed from Step 3 modelling was 21.4 µg a.s./kg dw sediment but an accumulation modelling performed by RMS UK resulted in an accumulated PEC of 95.7 µg/kg sediment.

Highest PECsw from the step 3 modelling performed with the most relevant application rate of 1x 94 g a.s./ha was 0.6 µg/L and highest PECsed was 5.02 µg/kg (2x94 g a.s./ha). Not all surface water scenarios were run with the most relevant application rate for Norway. Spray drift appeared to be the major contributing factor for most scenarios except for one, where run off was more significant.

A FOCUS step 4 modelling (using SWAN v 1.1.4), based on the results of the step 3 modelling and applying a 5 meter spray buffer zone, resulted in a maximum PECsw of 0.57 µg/L.

3.3.3 EFFECTS ON TERRESTRIAL ORGANISMS

Where there are indications that the plant protection product is more toxic than what can be explained by the content of the active substances (or studies are only conducted with the product), or identified metabolites are more toxic than the active substances, these calculations are included in the summary below. If this is not the case, these values and calculations are omitted.

3.3.3.1 *Mammals*

Bixafen has low acute toxicity (LD50: >2000 mg/kg bw/d) to mammals. TER_{acute} for the indicator species small herbivorous mammal and insectivorous mammal in cereals are estimated as 90 and 2419, respectively. These values do not exceed the trigger (<10). NOEC from reproductive study: 33.3 mg/kg bw/d.

$TER_{chronic}$ is estimated to be 115 and 4.7 for insectivorous mammal and small herbivorous mammal, respectively. The first tier risk assessment for the small herbivorous mammal has been refined using the EFSA (2009) birds and mammals guidance document, resulting in a $TER_{chronic}$ of 16. This value does not exceed the trigger (<5).

3.3.3.2 *Birds*

Bixafen has low acute toxicity (LD50: >2000 mg/kg bw/d) to birds. TER_{acute} for the indicator species in cereals (large herbivorous and insectivorous birds) is estimated as >284. This value does not exceed the trigger (<10). NOEC for reproduction: 30 mg/kg bw/d. $TER_{chronic}$ is estimated to be 12.9 and 10.6 for large herbivorous bird and insectivorous bird, respectively. These values do not exceed the trigger (<5).

3.3.3.3 *Bees*

Bixafen has low contact (LD50: >121 µg a.s./bee) and oral (LD50: >100 µg a.s./bee) toxicity to bees.

Hazard quotients for contact (Qhc) and oral exposure (Qho) are estimated to be 0.9 and 0.8, respectively. None of the hazard quotients exceed the trigger value (>50).

3.3.3.4 *Non-target arthropods*

Extended lab studies did not show effects above the trigger effect level of 50 % at relevant application rates.

3.3.3.5 *Earthworms*

Bixafen has low acute toxicity (LC50: 500 mg a.s./kg d.wt. soil) to earthworms. TER_{acute} is estimated to be 556. This value does not exceed the trigger (<10). The NOEC for bixafen is 20.8 mg a.s./kg d.w. soil. $TER_{chronic}$ is estimated to be 23. This value does not exceed the trigger (<5).

3.3.3.6 *Other soil macro organisms*

Since the soil DT90 for bixafen is >365 days, the toxicity of Aviator Xpro EC 225 has been tested on the springtail *F. candida*. The $NOEC_{reproduction}$ is 52 mg product/kg d.wt. soil and the TER is estimated to be 32. This value does not exceed the trigger (<5).

3.3.3.7 *Litter degradation*

When DT90f is > 365 days, testing on organic matter breakdown is triggered. Based on the DT90f of bixafen (>1000 days), a product containing bixafen as the active substance has been tested on litter degradation. The results of this study show negligible effects on organic matter breakdown.

3.3.4 EFFECTS ON AQUATIC ORGANISMS

Where there are indications that the plant protection product is more toxic than what can be explained by the content of the active substances (or studies are only conducted with the product), or identified metabolites are more toxic than the active substances, these calculations are included in the summary below. If this is not the case, these values and calculations are omitted. The TER calculations below are based on maximum PEC-values from FOCUS surface water modelling and the lowest acute (LC50 or EC50) or chronic (NOEC) values for the different organism groups and substances. All calculations are based on an application rate of 9.4 g bixafen/daa, which is the applied application rate in Norway. A tiered approach is applied. Step 2 is calculated for all tested substances, and if the TER fails the triggers, higher steps are calculated. The EU triggers for TER_{acute} and $TER_{long\text{-}term}$ are $\geq$100 and $\geq$10, respectively.

3.3.4.1 *Fish*

Bixafen shows very high to extremely high acute toxicity (96h LC50: 95-105 µg a.s./L) and very high chronic toxicity (33 d NOEC: 4.6 µg a.s./L). Aviator Xpro EC 225 is acutely toxic to rainbow trout (96h LC50: 1550 µg/L).

All acute TER calculations for bixafen pass the EU trigger based on Step 3 FOCUS surface water scenarios. Bixafen fail the EU trigger for long-term TER for Step 3, and need further refinement. Based on Step 4 calculations for other products/application rates, the risk is assumed to be acceptable with a 10 meter buffer zone.

3.3.4.2 *Invertebrates*

Bixafen is acutely toxic (48h EC50: 1200 µg a.s./L) and shows moderate chronic toxicity (EC50: 125 µg a.s./L) to daphnids. Aviator Xpro EC 225 is acutely toxic to daphnids (48h EC50: 3000 µg/L).

All TER calculations (both acute and long-term) for bixafen pass the EU trigger based on Step 2 FOCUS surface water scenarios.

3.3.4.3 *Sediment dwelling organisms*

Bixafen shows low to medium chronic toxicity to *Chironomus riparius* larvae (28 d NOEC: 16 µg a.s./L (spiked water) and 20 000 µg/kg (spiked sediment)).

All TER calculations for bixafen (both spiked water and spiked sediment) pass the EU trigger based on Step 2 FOCUS surface water scenarios. Even TER based on a calculation of PEC_{acc} after 20 years of use of bixafen pass the trigger.

3.3.4.4 *Aquatic plants*

No information.

3.3.4.5 *Algae*

Bixafen shows extremely high toxicity to green algae (72 h EC50: 60-97 µg a.s./L). Aviator Xpro EC 225 is acutely toxic to green algae (72h EC50: 1520 µg/L).

All TER calculations for bixafen pass the EU trigger based on Step 2 FOCUS surface water scenarios.

3.3.4.6 *Microorganisms*

No information.

3.3.4.7 *Microcosm/Mesocosm studies*

No information.

3.3.5 BIOCONCENTRATION

Bixafen shows a high potential for bioconcentration (BCF: 695) but a rapid depuration (CT50: 1.3 days).

3.4 DOSSIER QUALITY AND COMPLETENESS

The dossier is complete and is adequate as a basis for an evaluation of the active substance, metabolites and product.

4 Risk characterization

4.1 SUMMARY OF HUMAN TOXICITY/INHERENT PROPERTIES

In the terms of reference VKM was requested to consider the possible health risk for operators related to the properties of the active substance bixafen used in Aviator Xpro EC 225; in particular the relevance of the observed effects of bixafen on liver and coagulation parameters in rats and mice, the thyroid tumours and reproductive effects observed in rats, and the establishment of NOAELs and reference values (ADI, AOEL and ARfD).

4.1.1 THE EFFECTS SEEN IN LIVER, AND THE PERTURBATION OF COAGULATION PARAMETERS

Liver: VKM discussed the seriousness of the effects and concluded that the liver effects reported in sub-chronic and chronic studies in rats, dogs and mice should be considered as an adverse effect and relevant for humans. The effects included increased liver weight and centrilobular and panlobular hepatic hypertrophy in rats, mice and dogs, and an increased incidence of hepatocellular necrotic foci and single cell necrosis in liver in mice. The NOAELs for liver effects were 2.8 mg/kg bw/day (2-year study rat), 6.7 mg/kg bw/day (18-month study mice) and 10 mg/kg bw/day (1-year study dog). The NOAEL value from the 2-year rat study is used for deriving the ADI.

Perturbation of the coagulation parameters: VKM discussed the seriousness of the effects and concluded that the adverse effects on coagulating parameters should be considered as an adverse effect and of relevance for humans. Effects on coagulation parameters were reported in sub-chronic studies and included an increase in platelet counts in rats and dogs, and longer prothrombine time in rats. In the 28-day mouse study, one male was found dead in the high dose group on day 7, and all remaining males and three females were sacrificed on study day 8-14. One contributing factor to the death and severe conditions of the mice was internal bleeding. In a chronic study in mice, increase in platelet counts and decrease in haemoglobin and haematocrit were reported. Furthermore, in chronic studies in rats and mice, mortality was reported, and the deaths were attributed to a haemorrhagic syndrome. In the rat study, the pattern of mortality in male rats indicated a dose-and time depended relationship. The deaths were considered attributed to lack of Vitamin K in the diet. However, no deaths were reported in the unexposed group. The Vitamin K level in the diet was < 0.3 mg/kg while the recommended level is 1 mg/kg. The mortality in the mouse study was only reported in the high dose group, and was not considered related to low levels of Vitamin K in the diet.

4.1.2 COAGULATION PARAMETERS AND VITAMIN K DEFICIENCY IN THE DIET

Vitamin K in the diet was only measured in the 2-year rat study on bixafen. The analysis showed levels of vitamin K < 0.3 mg/kg. The haemorrhagic syndrome was by the notifier considered attributed to lack of vitamin K in the diet. However, no effects on coagulating parameters were reported in the unexposed control group receiving the same diet. Males were therefore prematurely sacrificed at approximately 25 weeks (117 mg/kg bw/day dose group) and 35 weeks (all remaining male rats). The female rats remained in the study, but the diet was supplemented with very high levels of vitamin K (15.7 ppm). For male rats, a new 2-year study was performed with very high vitamin K supplementation in the diet (8.2 to 10.6 ppm). No deaths were reported in this study. The level of 8.2 to 15.7 ppm vitamin K is in excess of the recommended level for vitamin K content in rodent diets, about 1 mg/kg .

It is not clear what levels of vitamin K in the diet are appropriate when testing a compound with anticoagulant properties in rodents. In the experiment with low vitamin K content in the diet, the animals in the unexposed control group showed no symptoms related to coagulation, while exposed animals in the high dose group suffered from haemorrhage and death. VKM concludes that the observed perturbations of the coagulating parameters are not likely to be explained by vitamin K deficiency in the diet. Experiments with very high concentrations of vitamin K in the diet should be interpreted with care in the evaluation of the toxic effects of suspected anticoagulants. It cannot be excluded that high doses of vitamin K may mask intrinsic effects of the test substance. Therefore, the adverse effects on coagulating parameters should be considered an adverse effect of bixafen.

4.1.3 RELEVANCE OF THE THYROID TUMOURS IN RAT STUDY

In female rats, an increase in thyroid follicular cell tumour incidence (combined adenoma & carcinoma) was reported. However, the increase was not significant and not dose-dependent. In male rats, no increase in thyroid follicular cell tumours was observed. Also in chronic studies in male and female mice, no thyroid follicular tumours were reported.

Since the induction of thyroid tumours was only reported in female rats, and the number was not significant and not dose-related, the data is not sufficient to suggest that bixafen has a tumour inducing potential.

4.1.4 REPRODUCTIVE EFFECTS IN RAT STUDY: FOETAL MORTALITY AND REDUCED BODY AND ORGAN WEIGHTS DURING LACTATION

In the two-generation study, F1 and F2 pup body weight was significantly reduced during lactation in the high dose group; in F1 pups starting on lactation day 7, and in F2 pups on lactation day 14. In the one-generation study in rats, high dose male and female pup body weight was also reduced during lactation; starting on day 4 with more pronounced declines throughout lactation. The pup body weight was not affected at time of birth. Since reductions in pup weight was seen on lactation day 4 in the dose ranging study, it is unlikely that this is caused by pup consumption of solid food. Therefore, it cannot be excluded that the reduced pup weight during lactation is mediated by the presence of test material in the dam's milk (Log Pow 3.3) or a change in suckling behaviour (the amount of milk produced by the dams or the natural status of the milk). Furthermore, bixafen is shown to be transferred to milk in a feeding study with dairy cows.

In the one-and two-generation studies, a significant reduction in relative organ weights (brain and spleen) were reported in male and female pups in the high dose group. This effect should be considered treatment related.

In the two-generation study, the number of stillborn F1 pups, the number of F1 litters with stillborn pups and the number of F2 litters with stillborn pups were increased in the high dose group when compared to concurrent controls, and were slightly outside the historical control data for the laboratory. However, there was no dose response between the F2 low dose and high dose groups. In the one-generation study no increase in stillbirths was observed at a higher dose-level than in the two-generation study. VKM is of the opinion that it cannot be excluded that exposure to bixafen has a direct effect on the number of stillborn pups in the F1 and F2 generation.

NOAELS from the two-generation study:

NOAEL parental: 3.3 and 3.64 mg/kg bw/day (male and female, respectively), based on effects in liver and thyroid in male and female rats, and seminal vesicle in males.

NOAEL reproductive toxicity: 27.3 and 30.3 mg/kg bw/day (male and female, respectively), based on increased numbers of stillborn pups.

4.1.5 EFFECTS IN RABBIT TERATOGENICITY STUDY

In the rabbit teratogenicity study the number of runts was increased at 400 mg/kg bw/day. Compared to controls, there was an increase in the number of foetuses and litters with visceral

variants and anomalies including short innominate arteries (variant) from 100 mg/kg bw/day which on a litter basis was slightly above the upper limit of the historical control data. This effect was also seen at 400 mg/kg bw/day; however a clear dose-response relationship could be masked by the high dam mortality at this dose level. Sub-clavian right artery (anomalies) was dose-dependently increased, and also above the upper limits of the historical control data at 400 mg/kg bw/day. Other visceral anomalies were also reported to be outside the historical control data at 400 mg/kg bw/day, including convoluted and dilated ureters (seen from 100 mg/kg bw/day, but only outside the historical control data at 400mg/kg bw/day) and dilated renal pelvis and enlarged kidney.

Skeletal anomalies reported included extra sternebral ossification sites that were significantly and dose-dependently increased from 100 mg/kg bw/day, and outside the historical control data.

The effects observed in the pups are considered treatment related, and should not be regarded as secondary effects related to maternal toxicity.

NOAELS from the teratogenicity study:

NOAEL maternal: 25 mg/kg bw/day based on reduced bodyweight gain, hair loss and reduced or no excreta and increased liver weight from 100 mg/kg bw/day.

NOAEL development: 25 mg/kg bw/day based on reduced foetal weight, increase in the percentage of litters with short innominate arteries, and extra sternebral ossification sites.

4.1.6 ESTABLISHMENT OF REFERENCE VALUES

NOAEL values:
VKM proposes a NOAEL of 2.0 mg/kg bw/day for setting of ADI based on the 2 year toxicity study in rat, and is of the opinion that the test substance-related increased incidences of multinucleated hepatocytes and hepatocellular hypertrophy, as well as increased incidence of thyroid follicular cell hypertrophy and colloid alteration, is considered relevant for humans.

VKM proposes a NOAEL of 12.9 mg/kg bw/day for setting AOEL based on a 90-day feeding study in rats, and is of the opinion that the test substance -related increase in hepatic centrilobular hypertrophy and thyroid follicular cell hypertrophy, is considered relevant for humans.

VKM proposes a NOAEL of 2.0 mg/kg bw/day for setting ARfD based on a developmental toxicity study in rats, and is of the opinion that the test substance-related reduced foetal weight is considered relevant for humans.

ADI
An ADI of 0.02 mg/kg bw/day is proposed for bixafen based on applying a 100-fold uncertainty factor to NOAEL of 2.0 mg /kg bw/day based on a 2 year feeding study in rats. The uncertainty factor accounts for interspecies extrapolation (10X) and intraspecies variability (10X).

AOEL
An AOEL of 0.13 mg/kg bw/day is proposed for bixafen based on applying a 100-fold uncertainty factor to the NOAEL of 12.9 mg /kg bw/day determined in the 90-day feeding study in rats. The NOAEL is based on the induction of hepatic centrilobular hypertrophy.

AR_fD
An AR_fD of 0.2 mg/kg bw/day is proposed for bixafen, based on applying a 100-fold uncertainty factor to the NOAEL of 20 mg/kg bw/day determined in a rat developmental toxicity study. The NOAEL is based on the observed reduced foetal weight.

4.2 HEALTH RISK CHARACTERIZATION

4.2.1 HEALTH RISK DUE TO HUMAN EXPOSURE

VKM has based the risk characterization for operators on the summary from the Norwegian Food Safety Authority (section 5.5), and related this to the suggested AOEL value as indicated here in section 2.1.

4.2.1.1 *Operator, worker and bystander exposure*

Operator exposure:

The AOEL for bixafen is highly exceeded without the use of personal protective equipment (PPE), but when gloves are used during mixing and loading the estimated exposure is below the AOEL.

Re-entry and bystander exposure:

Re-entry is not considered relevant for the intended use. Bystander exposure is calculated to be well below the AOEL.

4.2.2 HEALTH RISK DUE TO RESIDUES IN PRODUCTS FOR CONSUMPTION

Not included in the terms of reference.

4.3 ENVIRONMENTAL FATE ASSESSMENT

In the terms of reference it was stated that VKM should look at the fate and behaviour in the environment and the ecotoxicological effects and risks with regard to the properties of the active substance and the product. The Panel on plant protection products of the Norwegian Scientific Committee for Food Safety (VKM) has reviewed the actual documentation and points out the following inherent properties of the product, the active substances and possible metabolites:

4.3.1 DEGRADATION AND ACCUMULATION IN SOIL

Aerobic degradation studies in laboratory show that less than 10 % of bixafen was eliminated over the study duration (120 days). Half-life from laboratory studies was not calculated as the half-life had to be extrapolated beyond the study duration, but estimated to be >1 year. One metabolite, M44, was identified and detected at maximum 2.9 % of applied radioactive dose. This is the same metabolite as from fluxapyroxad (BAS 700F) (EFSA, 2012a).

From field studies with bixafen in four locations in Europe, data from Sweden and Germany show especially slow dissipation. The DT50 value from the field dissipation trial in Germany was >1000 days for most of the kinetic models before normalization. The geometric mean DT50 value for normalised field dissipation from the four locations was 249 days.

The long half-lives indicate a high potential for accumulation in soil, and after 6 years of repeated use of bixafen in the on-going study in Germany, a plateau concentration was still not reached (2005-2010). EFSA (2012b) concluded that data on persistence in soil was not sufficient. Model calculations by Norwegian Food Safety Authority with the Finnish PEC soil calculator using worst case un-normalised field DT50 showed that a plateau was not reached after 20 years of continuous use. The panel concludes that bixafen is likely to be persistent in Norwegian soils with an associated risk of accumulation after repeated use.

4.3.2 MOBILITY IN SOIL AND LEACHING TO GROUNDWATER

Sorption studies indicate very high sorption of bixafen in soil, and leaching to groundwater is not likely. No data on the mobility of M44 has been submitted, but the metabolite M44 has been shown to exhibit high to very high mobility in studies on the active substance fluxapyroxad. Results from the groundwater modelling with M44show that the metabolite will leach to groundwater at levels above 0.1 mg/l in all nine FOCUS scenarios and above 0.75 µg/L in three of these scenarios (EFSA, 2012b). VKM concludes that the metabolite M44 has a potential for leaching to groundwater.

4.3.3 SOIL CONCENTRATIONS

The substance is applied maximum two times each year. Following the second application, initial concentrations in soil (PIECsoil) have been calculated at 0.125 mg/kg. Following multiple year use, a maximum PECsoil has been calculated at 0.90 mg/kg (Finnish PEC calculator; 20 year repeated application). VKM supports the use of the worst case non-normalised DT50 value from the northern-European field studies as input to long-term accumulation assessment.

4.3.4 SURFACE WATER AND SEDIMENT CONCENTRATIONS

Concentration in surface water and sediments are calculated using FOCUS scenarios. The highest concentration in surface water with application rates relevant for Norway was 0.6 µg/L and 5.0 µg/kg in sediments. Spray-drift is considered to be the major contributing factor, except for one scenario where runoff was more significant. None of the locations used in FOCUS scenarios are very steep (a few % slope, compared to >10 % in many areas in Norway). Steep slopes in combination with particle-sorbed pesticides typically give a high runoff contribution due to erosion.

Similar to in soils, bixafen shows a very slow elimination from sediments. Accumulation in sediment cannot be excluded, with a maximum PEC estimated at 95.7 ug/kg after 20 years (United Kingdom, 2011). A default DT50 value of > 1000 days was used for calculation of PECsediment. The panel considers these maximum PEC values to be relevant for aquatic risk assessment.

Assessment of criteria for classification of bixafen as a Persistent Organic Pollutant (POP) has been screened. Bixafen meets the criteria for persistence and adverse effects with toxicity to aquatic organisms. Bixafen also showed potential for bioaccumulation in a test with fish (BCF of 695), but the value was lower than the threshold value of 1000. Bixafen does not meet the criteria for potential for long range transport (United Kingdom, 2012).

4.4 ENVIRONMENTAL RISK CHARACTERIZATION

The Panel's risk characterization of the product's ecotoxicological effects on terrestrial and aquatic organisms is based on the summary from the Norwegian Food Safety Authority presented in section 3.4.3-3.4.4 and exposure-, dose/response assessments and risk scale described in section 2.2. In additions documents from EFSA (2012a, 2012b) and Draft Assessment Reports (DAR) (United Kingdom, 2011 and 2012) has been used.

4.4.1 EFFECTS AND RISKS TO TERRESTRIAL ORGANISMS

Based on available information, there is minimal risk for toxic effects of bixafen to mammals, birds, bees, earthworms, plants and soil microorganisms with the proposed application regime. None of the trigger values for these organisms are exceeded.

The panel concludes that there is minimal risk for toxic effects of bixafen to terrestrial organisms with the proposed application regime.

4.4.2 EFFECTS AND RISK TO AQUATIC ORGANISMS

Bixafen is very toxic to aquatic organisms. Trigger values for chronic toxicity to fish was exceeded for exposure calculations with FOCUS step 3 without mitigation measures. When a 5 m spray drift bufferzone was established, the majority of the FOCUS scenarios indicated minimal risk to fish. However, the runoff scenario for stream still exceeded the relevant trigger for fish, suggesting that a 10 m buffer zone is necessary to achieve minimal risk.

The Panel concludes that there is minimal risk for toxic effects of bixafen to aquatic organisms taking into account the suggested mitigation of a 10 m bufferzone.

4.5 QUALITY OF THE SUBMITTED DOCUMENTATION

VKM is of the opinion that the documentation submitted to VKM is adequate as a basis for an evaluation of the active substance, the metabolites, and for the technical material.

5 Conclusion

5.1 HEALTH

VKM concluded that the liver effects reported in sub-chronic and chronic studies in rats, dogs and mice exposed to bixafen, as well as the effects on coagulating parameters, should be considered adverse and of relevance to humans.

It is the opinion of VKM that the thyroid follicular cell tumours reported in female rats exposed to bixafen is not sufficient to suggest that bixafen has a tumour inducing potential.

It is further the opinion of VKM that it cannot be excluded that the reduced pup weight during lactation in the two-generation study is mediated by bixafen via the milk, and that bixafen has a direct effect on the number of stillborn pups in the F1 and F2 generation.

Finally, the pup developmental variants and anomalies reported in the teratogenicity study are considered treatment related, and not a secondary effects related to maternal toxicity.

VKM proposes:

- NOAEL of 2.0 mg/kg bw/day based on a 2 year feeding study in rats.
- ADI: 0.02 mg/kg bw/day
- AOEL: 0.13 mg/kg bw/day
- ARfD: 0.2 mg/kg bw/day

Risk calculations show minimal risk if personal protective equipment is used.

5.2 ENVIRONMENT

Bixafen is shown to be persistent in soil. VKM considers the results from a field study on a German site and the Finnish PEC calculator to be relevant and concludes that repeated annual applications can cause accumulation in soil under Norwegian conditions. There is also a potential for groundwater contamination from leaching of the metabolite M44.

VKM has concluded that the use of bixafen as an ingredient in Aviator Xpro EC with the proposed application regime in Norway will represent a minimal risk for toxic effects to terrestrial organisms.

The toxicity of bixafen to aquatic organisms is high, and minimal risk of effects in surface waters can be achieved only if risk mitigation measures with bufferzones of 10 m are applied.

6 Documentation

The documentation submitted by the applicant in the process of application for registration of Aviator Xpro EC 225 has been compiled and evaluated by The Norwegian Food Safety Authority. (www.Mattilsynet.no)

In addition, VKM has performed a combined literature search in PubMed, TOXNET and Embase using the name of the active substance (bixafen). The resulting references has been considered by VKM and used in the risk assessment when relevant.

References

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