Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

Risk assessment of the fungicide Luna Privilege with the active substance fluopyram

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

Date: 19.02.2014

Doc. no.: 13-207

ISBN: 978-82-8259-124-9

VKM Report 2014: 17

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Summary

Luna Privilege is a new fungicide for use in apples, pears, outdoor and indoor strawberries, outdoor and indoor lettuces, peas, beans and indoor tomatoes, and contains the new active substance fluopyram.

VKM was requested by the Norwegian Food Safety Authority to consider the possible health risk for operators related to the properties of Luna Privilege and fluopyram; in particular to evaluate the potential for bioaccumulation, reproductive and neurotoxic effects, and discuss possible mechanisms involved in liver and thyroid tumor formation observed in rats, and the establishment of NOAELs and reference values.

VKM was also asked to evaluate the fate and behaviour of fluopyram in the environment, and the ecotoxicological effects and risks related to its use, in particular the potential for groundwater contamination, safety margins and possible effects on birds and aquatic organisms.

The assessment was finalized in a meeting on December 13. 2013 by VKM's Panel on Plant Protection Products.

VKM's conclusions are as follows:

Health

It is the opinion of VKM that:

- The active ingredient fluopyram has low potential for bioaccumulation, and the data do not suggest a sex-specific excretion.
- An *in vivo* Comet Assay in rat liver could help to further elucidate the genotoxic potential of fluopyram.
- It can not be excluded that the reported incidence of "gall bladder absent" is treatment related.
- NOAEL for the 90-day feeding study in rats should be set to 3.06 mg/kg bw/day, resulting in an AOEL of 0.03 mg/kg bw/day.
- The "dumb-bell or incomplete ossification and/or bipartite/normal cartilage" should be considered as a malformation and regarded as treatment related.
- The time points used for neurotoxic measurements are not optimal to detect neurotoxic effects from acute exposure, since the time window between the first and second measurements is too long.
- The studies where effects of fluopyram and phenobarbital are compared can not be used to exclude human relevance of the tumor-inducing effect of fluopyram in the liver of female rats.
- The results from the mechanistic studies are insufficient to support the proposed mode of action for the induction of thyroid follicular cell tumors in male mice, and thus the induction of thyroid tumors in male mice could be relevant for humans.

VKM proposes:

- NOAEL of 1.2 mg/kg bw/day based on a 2 year feeding study in rats.
- ADI: 0.012 mg/kg bw/day
- AOEL: 0.03 mg/kg bw/day
- ARfD: 0.25 mg/kg bw/day

Risk calculations for field use of Luna Privilege show minimal risk if personal protective equipment is used. The AOEL of fluopyram for greenhouse use is not exceeded, even without protective equipment. Re-entry and bystander exposure is calculated to be well below the AOEL.

Environment

It is the opinion of VKM that:

- Worst case degradation rates from laboratory studies should preferably be used to calculate PECsoil values for fluopyram.
- Both fluopyram and fluopyram-7-hydroxy have a high potential for groundwater contamination.
- The efficacy of buffer zones needs to be considered on a case-by-case basis, and further validation of values for efficacy from the model simulation is necessary.
- It is further the opinion of VKM that all the refinements used in the risk assessment for birds are relevant. Since the TER values estimated for all crops except for orchards are below the trigger following refinements, it is the view of VKM that the data indicate medium risk for strawberries and pulses, and high risk for lettuce in open field.
- The use of LC50 values for fluopyram in the TER calculations with a TER trigger value of 100 is overly conservative, and a reduction of the acute trigger for both invertebrates and fish from 100 to 10 for such calculations are suggested.
- The trigger for acute toxicity is not exceeded for any of the crops. For chronic toxicity, VKM concludes that there is a moderate risk for effects on fish when Luna Privilege is applied to beans/strawberries without the use of a vegetated mitigation buffer-strip.

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 October 24, 2013 for VKM to perform a risk assessment on use of the new fungicide Luna Privilege containing the new active substance fluopyram, for use in apples, pears, outdoor and indoor strawberries, outdoor and indoor lettuces, peas, beans and indoor tomatoes. The risk assessment was finalized in January 2014.

Terms of reference

Luna Privilege is a new product containing the new active substance fluopyram. The intended use is as a fungicide in apples, pears, outdoor and indoor strawberries, outdoor and indoor lettuces, peas, beans and indoor tomatoes.

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 Luna Privilege and fluopyram. The Panel is in particular asked to look at the following:
    - The potential for bioaccumulation based on the long half life (73 h) of pyridyl-labeled fluopyram in female rats.
    - The necessity of additional in vivo study to investigate organ specific genotoxicity due to the oncogenic effect observed in the rat and mouse studies.
    - Establishment of the NOAEL for the 90-day feeding study in rats and the reference value (AOEL).
    - A higher incidence of the variations “at least one thoracic centrum: split/split cartilage and “at least one thoracic centrum: dumbbell and/or bipartite/normal cartilage observed in the rat developmental toxicity study, and if these are considered to be malformations.
    - The malformation “gall bladder absent” observed in the rabbit developmental toxicity study – is this treatment related?
    - In the acute neurotoxicity study, FOB and motor activity measurements were performed on four occasions: one week prior to treatment, approximately 1 hour, 7 days and 14 days following treatment. However, the toxicokinetic studies have shown that Tmax for high dose was 35 h in males and 42 h in females. Were these time points for the measurements optimal in this study?
    - The phenobarbital mechanism of action proposed for the tumours seen in the liver of female rats and if this is sufficiently supported by the submitted mechanistic studies.
    - The mechanism of action proposed for the thyroid tumours seen in the male mice and if this is sufficiently supported by the submitted mechanistic studies.

    - The genotoxicity as a mechanism of action for the tumours observed in the liver and thyroid.
- The fate and behaviour in the environment and the ecotoxicological effects and risks with regard to the properties of Luna Privilege and fluopyram. The Panel is in particular asked to look at the following:
    - The relevance of the field study conducted in Staffanstorp, Sweden, for Norwegian conditions. Is it acceptable to use the results (DT50) from this study to calculate PECsoil?
    - The potential for groundwater contamination for both fluopyram and fluopyram-7-hydroxy. MACRO results are not completed yet, and results will be provided to you as soon as they are ready.
    - The relevance of using a run-off buffer as a mitigation measure in Step 4. The values used for run-off reduction in a 10-12 m vegetated buffer strip are given in in the FOCUS guidance document on landscape and mitigation, vol. 1 (2007), Table 7, p. 33 . Can these values be considered relevant for Norway?
    - The refinements used in the risk assessment for birds.
    - The TER calculations for fish and aquatic invertebrates, specifically the consequences of using LC50 values based on either no effect in the highest tested concentration or surrogate LC50 as endpoints in the acute assessment, especially in the context of the water solubility; and the inclusion of a run-off buffer in the Step 4 PEC.

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 Luna Privilege 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)

Luna Privilege is a new fungicide, and fluopyram is a new active substance for Norway. Fluopyram was approved in the EU in August 2013.

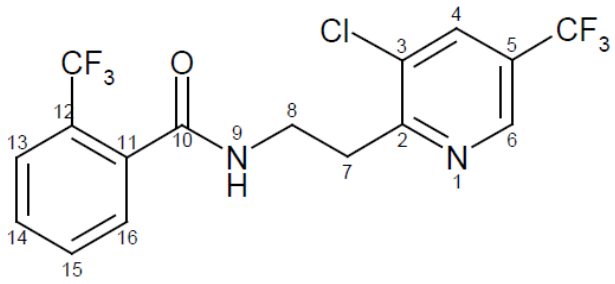
3.1 EFFICACY

Luna Privilege is an aqueous suspension concentrate (SC) containing 500 g/L of fluopyram. The application is for use against powdery mildews in apples and pears, strawberries and tomatoes, grey mould in strawberries, tomatoes, lettuce, peas and beans and white mold in lettuce, peas and beans. Side effect on apple scab. Recommended use is 2-4 applications per year, depending on diseases and cultures.

There is a need for new plant protection products to avoid development of resistance. Although fluopyram is a so called SDHI fungicide, cross resistance to boscalid, another SDHI fungicide approved in Norway, has not been discovered internationally. Furthermore, in pome fruit, tomatoes and cucumbers, there are no SDHIs available, and thus fluopyram is a new effective compound against several important diseases.

Strawberries is the largest of the use areas, hence the max dose of strawberries, 0,6L/Ha = 60 ml /daa = NAD. (30 g/daa fluopyram). Apples have a similar area, but powdery mildew is less frequent so Luna Privilege will probably not be relevant on all apple area.

3.2 IDENTITY AND PHYSICAL/CHEMICAL DATA

Product name	Luna Privilege
Active substance	Fluopyram
Formulation	SC – Aqueous Suspension Concentrate
Concentration of active substance	500 g/L
IUPAC-name	N-{2-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]ethyl}-2-(trifluoromethyl)benzamide
CAS number	658066-35-4
Structural formula	
Molecular weight	396.72
Solubility in water	Medium: 16 mg/L (20 °C, no pH dependency)

Vapour pressure	Low: 1.2 x 10^{-6} Pa (20 °C)
Henrys law constant	Low: 2.98 x 10^{-5} Pa m^3/mol
log Pow	High: 3.3 (20 °C)
pKa	No pKa value could be detected in the range of 2<pKa<12.

3.3 MAMMALIAN TOXICOLOGY

3.3.1 FLUOPYRAM

3.3.1.1 *Toxicokinetic studies*

The kinetic behaviour and metabolism of fluopyram were investigated in rats. Five different studies were performed: two ADME studies with the two different (phenyl- and pyridyl-) labels, two quantitative whole body autoradiographic studies with the two different labels and an organ depletion study with pyridyl labeled fluopyram.

Absorption: Fluopyram was rapidly absorbed from the gastrointestinal tract following oral administration. The absorption rate was 93% and 97.7% of the total recovered radioactivity of phenyl- and pyridyl labeled fluopyram, respectively, leading to the conclusion that the administered dose was absorbed virtually completely and became systemically bioavailable.

Distribution: Following absorption from the GIT, fluopyram was widely distributed. Organs with highest residues were the liver, the kidneys, Harderian gland and, in some studies and to a lesser extent, erythrocytes, adrenals, thyroid, ovaries and carcass. Because of a rather higher log $P_{O/W}$ value of 3.3 and relatively high total residues after 168 hours in the single dose studies, a certain potential for bioaccumulation cannot be excluded. Sex specific differences in toxicokinetics were observed; systemic exposure was higher and enterohepatic circulation more pronounced in females.

Metabolism: The analysis of metabolism revealed a number of metabolites including fluopyram-7-hydroxy and -8-hydroxy, fluopyram-pyridyl-acetic acid and fluopyram-benzamide being the most abundant. The benzamide metabolite and a fluopyram-olefine are of potential toxicological concern.

Excretion: 90.6% - 99.3% of the administered phenyl labeled fluopyram was excreted at 168 h post administration while 98% of the administered pyridyl labeled fluopyram at 72 h post administration via urine and feces. However, excretion was not complete because of the rather high radioactive residues in the body at sacrifice and still ongoing renal excretion. There were remarkable differences in the toxicokinetic data depending on the part of the molecule that had been radiolabeled. These results were explained by molecular cleavage of fluopyram and different biokinetic behaviour of the two labels especially in terms of urinary excretion. In addition, routes of excretion were slightly different depending on the label; when labeled in the phenyl ring, excretion via the feces accounted for 47-64% whereas renal excretion ranged from 35-45 % in both sexes. With the pyridyl-label, excretion was 53% fecal and 45% urinary in male rats but 39% fecal and 60% urinary in females. Exhalation was negligible in all tests.

3.3.1.2 *Acute toxicity*

Fluopyram is of low acute toxicity after oral, dermal and inhalation exposure, and therefore no classification is required.

3.3.1.3 *Irritation and sensitisation*

Fluopyram is not considered to be neither a skin- or eye irritant nor a skin sensitizer.

3.3.1.4 *Genotoxicity*

All *in vitro* and *in vivo* genotoxicity studies were shown to be negative. However, due to the oncogenic effect seen in the rat and mice studies, a second *in vivo* test should have been conducted to investigate organ specific genotoxicity.

3.3.1.5 *Sub-chronic toxicity*

Body weight and food consumption were compromised in nearly all feeding studies at higher dose. Palatability problems were noted in dogs.

The liver proved to be the main target organ in all three species. Hepatotoxicity became apparent by a dose-related increase in organ weight, alterations of clinical chemical parameters and histopathological findinngs such as hypertrophy or vacuolation. In addition, there was evidence for induction of microsomal liver enzymes as indicated by a dose-related increase in total cytochrome P-450, BROD and PROD activities in the 28-day feeding study in rats at the two upper dose levels. Liver effects were also observed following dermal administration of the limit dose of 1000 mg/kg bw/day to rats. Another common target organ was the blood with changes in red blood cell parameters, an extended prothrombin time and an increase in platelet count in the oral and dermal studies in rats.

The pathological changes in kidneys (organ weight increase associated with hyaline droplet nephropathy) were confined to the studies in rats. The nephropathy in male rats was characterised by basophilic tubules, hyaline droplets in the proximal tubule and granular cast in the medulla and was not reversible after one month of recovery. It was assumed to be due to accumulation of $\alpha_{2\mu}$-globulin in the proximal tubules, i.e., a toxic mechanism that is rat-specific and of less relevance to human. In contrast, the mechanism causing thyroid changes (higher organ weight, follicular cell hypertrophy) in rats is not that clear because they were accompanied by an increase in TSH, T3 and occasionally also T4 levels. Usually, the rodent-specific mode of action of many chemicals is by enhanced catabolism of T3 and T4 (i.e., lower plasma/serum levels) due to induced microsomal liver enzymes that, via a feed back mechanism, results in an increase in TSH production with subsequent stimulation and proliferation of the thyroid. A similar pathological finding in male dogs (diffuse follicular epithelial hypertrophy) was observed in the one-year study.

Adrenal glands were affected only in mice and these findings (organ weight increase, decrease in ceroid pigmentation, hypertrophy of the *Zona fasciculata* and cortical vacuolation) were confined to the high dose levels.

In the dog studies, decreased thymus weight in females and decreased spleen weight in males were observed. The thymus and the spleen are the lymphoid organs and they play an important part in the immune system. Thus, the immunotoxic effect of fluopyram cannot be excluded.

3.3.1.6 *Chronic toxicity and carcinogenicity*

In the 2-year oral toxicity study in rats, there was a statistically significant increase in mortality in males at 750/375 ppm during the study and after 24 months, although no clear cause for these premature deaths could be established. At the highest dose level of 750/375 in males or 1500 ppm in females, mean body weights were significantly reduced at various times throughout the study. Main target organs were the liver, the kidneys and the thyroid gland but also the eyes. Liver toxicity became apparent by an increase in organ weight at the two upper dose levels in male rats and in the highest dose group in females that was sometimes accompanied by gross pathological findings such as nodules/masses which correlated histologically with neoplastic changes. At the end of the 2-year carcinogenicity

phase, the incidence of liver cell tumours (carcinoma and adenoma) was significantly increased in females receiving 1500 ppm (equivalent to 89 mg/kg bw/day). The combined incidence of female rats with benign and malign liver tumours was 11 (including 3 animals with carcinoma) as compared to 2 in each of the control, low and mid dose groups.

Dietary administration of fluopyram over 18 months to the C57BL/6J mouse resulted in toxic effects on the liver, the kidneys and the thyroid at the top dose level of 750 ppm (equivalent to 105 mg/kg bw/day in males and 129 mg/kg bw/day in females). In male mice, higher incidence of follicular cell adenoma in the thyroid gland was observed at that dose level. Non-neoplastic changes in the liver in both sexes and in the thyroid gland in males were also seen at the mid dose level of 150 ppm (equivalent to 20.9 mg/kg bw/day in males and 26.8 mg/kg bw/day in females).

3.3.1.7 *Reproductive and developmental toxicity*

In the two-generation reproduction study in rats, systemic effects in male rats were confined to the top dose level of 1200 ppm. Liver and kidney toxicity at this dose became apparent by altered clinical chemistry parameters (increase in creatinine, total protein, albumin and urea nitrogen), higher kidney weights associated with a more frequent occurrence of protein droplet nephropathy and lymphocytic infiltration, and increased liver weights associated with centrilobular hypertrophy. In females, at 1200 ppm, a decline in body weight and/or body weight gain during the premating period and during gestation in the P-generation was noted. In contrast, body weight and food consumption were increased during gestation in the F_1-generation. Further findings comprised an increase in cholesterol level and in white blood cell and monocyte absolute cell counts in the F_1-generation, lower hemoglobin and/or hematocrit values in the P- and/or F_1-generation, higher liver weights associated with centrilobular hypertrophy and minimal to slight lung alveolar macrophages in the P- and/or F_1-generation. Based on these observations, the parental systemic NOAEL was 220 ppm (corresponding to 14.5 mg/kg bw/day in males and 17.2 mg/kg bw/day in females). The reproductive NOAEL was 1200 ppm in both males and females (82.8 mg/kg bw/day in males and 93.1 mg/kg bw/day females) because no reproductive findings were observed up to the highest dose tested. In the offspring, effects on pup body weight and body weight gain at the highest dose level of 1200 ppm might be secondary to maternal toxicity. In line with that, a slight delay in preputial separation was observed. A decrease in spleen and thymus weights in pups might indicate an adverse effect on the immune system. However, since no other immune parameters were affected and these effects were small in extent, a study on developmental immunotoxicity was not regarded necessary by the notifier and the RMS. Nonetheless, the offspring NOAEL was 220 ppm (14.5 mg/kg bw/day).

In the rat developmental toxicity study, there were no unscheduled mortalities or treatment-related clinical signs in the dams. At the highest and mid dose levels of 450 and 150 mg/kg bw/day, dams did not gain weight between GD 6-8. Thereafter, body weight and body weight gain remained lower throughout the study and food consumption was reduced. At necropsy, a dose-related significant increase in liver weight was noted and diffuse centrilobular hepatocellular hypertrophy was observed in a majority of dams. At the top dose level, hepatomegaly was noted in 4 females. The NOAEL for maternal toxicity was 30 mg/kg bw/day in this study, in spite of a transient reduction in maternal body weight gain and food consumption during the first three days of treatment (GD 6-8).

In the group receiving this dose, mean fetal body weights were by 5% lower than in the controls. Litter parameters were not affected but there was an increase in the incidence of a few visceral (‘thymic remnant present’ and ‘ureter convoluted and/or dilated’), and skeletal variations (‘at least one thoracic centrum split/split cartilage’ and ‘at least one thoracic

centrum dumbbell and/or bipartite/normal cartilage'). The low dose level of 30 mg/kg bw/day was considered the fetal NOAEL.

In the developmental toxicity study in rabbits, there were no treatment-related maternal deaths or clinical signs. At the high dose level of 75 mg/kg bw/day, mean body weight gain and food consumption were reduced in comparison to controls. At necropsy, no treatment-related macroscopic findings were noted. Mean fetal body weight was 11% lower at this dose. In line with that, individual and litter incidence of very small fetuses (classified as 'runts') was higher. At 75 mg/kg bw/day, there were two fetuses from separate litters with the malformation 'gall bladder absent', compared to no instance in the current control group. Thus, the mid dose level of 25 mg/kg bw/day was considered the NOAEL for both maternal and developmental toxicity.

3.3.1.8 *Neurotoxicity*

In the acute neurotoxicity study in rats, effects in males and/or females consisted of decreased motor and locomotor activity on the day of treatment, urine stain, and decreased body temperature. The NOAEL of 125 mg/kg bw was established for male rats whereas in females motor and locomotor activity was still impaired at this lowest dose level. Therefore, a follow-up study was conducted under the same conditions but only in females. Since slight decreases in (loco) motor activity became apparent at 100 mg/kg bw, the next lower dose of 50 mg/kg bw was considered the NOAEL for females.

In the 90-day neurotoxicity study in rats, no evidence of neurotoxicity was observed at any treatment level. Treatment-related findings of general toxicity at 500 and 2500 ppm consisted of decreases in body weight, total body weight gain and food consumption in males and females, some alterations in clinical chemistry and hematological parameters and an increase in the organ weights of liver, thyroid and kidneys. Thus, the low dose of 100 ppm (corresponding to a mean daily intake of about 6.69 mg/kg bw in males and 8.05 mg/kg bw in females) was considered as the NOAEL in this study.

3.3.1.9 *Special studies*

Several mechanistic studies were conducted to clarify the mechanism behind tumour formation in the liver of female rats and in the thyroid of male mice. Based on these studies the EU RMS concluded that the tumours in the thyroid of male mice should be considered as non-relevant for humans, while the tumours seen in the liver of female rats should be considered as relevant for humans. The US EPA and PMRA in Canada found, however, the results of the mechanistic studies insufficient to support the proposed mode of action for the induction of liver tumours in female rats or thyroid follicular cell tumors in male mice, and considered both tumour types as relevant for humans.

3.3.1.10 *Classification and labeling*

The proposed classification by the RMS and EFSA is Xn; Carc. Cat. 3, R40 (Limited evidence of a carcinogenic effect) (Carc. Cat. 2, H351 Suspected of causing cancer according to CLP). A classification in Carc. Cat. R45 May cause cancer (Carc. Cat. 1b, H350 May cause cancer according to CLP) is however be warranted based on the occurrence of tumours in two species.

3.3.1.11 *Reference values*

ADI: The ADI is 0.012 mg/kg bw/day based on the NOAEL of 1.2 mg/kg bw/day from the 2-year feeding study in rats. An UF of 100 is applied. (EFSA, 2013)

AOEL: EFSA has proposed that the AOEL is 0.05 mg/kg bw/day based the NOAEL of 5.4 mg/kg bw/day from the 90-day feeding study in mice (UF of 100). However, we propose the lower AOEL of 0.03 mg/kg bw/day based on the NOAEL of 3.06 mg/kg bw/day from the 90-day feeding study in rats (UF of 100).

ARfD: The ARfD is 0.5 mg/kg bw based on the NOAEL of 50 mg/kg bw from the acute neurotoxicity study in female rats. An UF of 100 is applied. (EFSA, 2013)

3.3.1.12 *Metabolites*

Two metabolites of fluopyram (fluopyram-pyridyl-carboxylic acid, AE C657188, and fluopyram-methyl-sulfoxide, AE 1344122) occurring in plants were investigated for acute oral toxicity study, *in vitro* genotoxicity tests and a 28-day short term toxicity study. These metabolites have not been found in the rat metabolism studies. Based on these studies it is concluded that the two metabolites had a lower toxicity when compared to fluopyram.

3.3.1.13 *Co-formulants*

Luna Privilege contains co-formulants that are responsible for the eye and skin irritation.

3.3.2 LUNA PRIVILEGE SC 500

3.3.2.1 *Acute toxicity*

Luna Privilege has low toxicity by oral, dermal or inhalation exposure.

3.3.2.2 *Irritation and sensitization*

Luna Privilege is found to be neither a skin- or eye irritant nor a skin sensitiser.

3.3.2.3 *Dermal absorption*

A generally low dermal absorption of fluopyram as a concentrate and a representative spray dilution was established when tested both *in vivo* on rat skin and *in vitro* on human and rat skin. The *in vitro* study showed that rat skin was more permeable than human skin, as with most substances. Furthermore, dermal absorption of the dilution was higher than that of the concentrate in both studies. Based on the results from the “triple pack”, dermal absorption values of 1% for the concentrate and 3% for the dilution are proposed.

3.3.2.4 *Operator, worker and bystander exposure*

Operator exposure to fluopyram during mixing, loading and spraying in the field will slightly exceed the AOEL if no PPE is used. However, the estimated exposure will be below the AOEL when PPE (gloves) are applied. On the contrary, operator exposure during mixing, loading and spraying in greenhouses will not exceed the AOEL, even if no PPE is used. Furthermore, bystander and worker exposures will be below the AOEL.

3.4 RESIDUES IN FOOD OR FEED

Residues are not discussed in this report.

3.5 ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL EFFECTS

The environmental assessment only covers outdoor field uses.

3.5.1 ENVIRONMENTAL FATE AND BEHAVIOUR

3.5.1.1 *Degradation in soil*

Fluopyram is hydroxylated to form the metabolite fluopyram-7-hydroxy (max 4.2 % of applied radioactivity, AR). Fluopyram-7-hydroxy in turn is cleaved to form the metabolites pyridyl-carboxylic acid (max. 0.7 % AR), containing the pyridine ring, and benzamide (max. 1.1 % AR) containing the phenyl ring. The pyridyl-carboxylic acid is metabolised to methyl-sulfoxide (max. 1.0 % AR). Microbial breakdown of the phenyl ring leads to the formation of CO2.

The aerobic rate of degradation of fluopyram in the laboratory was best described with SFO kinetics in four of five soils, the last soil requiring the use of double first order in parallel (DFOP) kinetics. The degradation of fluopyram can be characterised as moderate to low with DT50 162-746 days (geometric (geo.) mean DT50: 290 days), DT90 538- >1000 days. DT50 values exceeded the study duration in all soils. Thus, estimated DT50 and also DT90 values must be regarded as highly uncertain. The degradation rate of the metabolite fluopyram-7-hydroxy was well described with SFO kinetics and its degradation rate was medium to high with DT50 5.8-18 days (geo. mean 11 days), DT90 16-59 days.

Bound residues reached levels of about 15% AR. Mineralisation to CO2 reached levels of 27 % AR.

Under anaerobic conditions the SFO DT50 of fluopyram was > 1000 days and fluopyram is, therefore, considered stable under anaerobic conditions in soil. No major transformation products were detected.

Photolysis on soil surfaces is not considered to be an important route of transformation of fluopyram.

The field dissipation of fluopyram from soil under European field conditions was investigated at six sites in bare soil plots in Burscheid, Germany (silt loam), Little Shelford, United Kingdom (sandy loam), Staffanstorp, Sweden (loam), Vatteville, Northern France (silt loam), Vilobi d'Onyar, Spain (loam) and in Albaro, Italy (silt loam). Only the results from Germany, UK and Sweden are considered for Norway, as the other studies are not considered relevant. Fluopyram was applied once pre-emergence at a rate of 250 g/ha, which is lower than the maximum dose according to the Norwegian GAP (1x300 or 2x250 g/ha). The DT50 values indicate that fluopyram has a moderate rate of dissipation, DT50 145-179 days (geo. mean 162 days). The DT90 values were > 1000 days in all the North European studies and exceeded the study duration. Leaching might not be important at these sites, as there was no detection of residues below 30 cm.

Interim results from a soil accumulation study with sites in France and Germany indicated that fluopyram has potential for accumulation in soil under field conditions. However, the soils were not considered relevant for Norway due to a high sand content (only the German site) and low organic carbon content.

3.5.1.2 *Sorption/mobility*

The adsorption of fluopyram can be classified as medium, Kf: 2.94-6.82 L/kg (arithmetic mean 4.41 L/kg), Koc(ads): 233-400 L/kg (arithmetic mean 280 L/kg),1/n: 0.77-0.85 (arithmetic mean 0.83). The adsorption of fluopyram-7-hydroxy can be classified as moderate to medium, Kf(ads): 0.99-2.39 L/kg (arithmetic mean 1.52 L/kg), Koc(ads): 85-149 L/kg (arithmetic mean 103 L/kg), 1/n: 0.91-0.94 (arithmetic mean 0.93). The desorption Kd(des) of the 7-hydroxy metabolite ranged from 3.38 to 5.97L/kg (arithmetic mean 4.21 L/kg) and the Koc(des) values ranged from 237 to 373 L/kg (arithmetic mean 291 L/kg). Koc(des) values

were more than two times higher than the Koc(ads) values, indicating a strengthened binding of the test material once adsorbed to the soil (irreversible binding).

3.5.1.3 *Degradation in water*

Fluopyram is hydrolytically stable under acidic, neutral and alkaline conditions (pH 4, 7 and 9), and no major degradation products were detected.

Aquatic photolysis is not an important route of transformation for fluopyram in the aquatic environment and no major metabolites are expected to be formed in the natural sediment/water systems.

Fluopyram is considered not readily biodegradable.

Aerobic degradation of fluopyram was studied in two pond water-sediment systems (sandy and clay). The half-life decline times were described by SFO kinetics for the total sediment/water systems and by DFOP for the water phase. In the water phase the dissipation rate was medium, DT50 14-26 days. In the total system the dissipation rate was low, DT50 >648 days. Fluopyram partitioned significantly from water to the sediment under aerobic conditions. Extractable residues in sediment increased to 64 % AR in the first test system and to 69 % AR in the second test system during the study period (120 days). Residues in water decreased to 28 % AR in the first test system and to 21 % AR in the second test system. No major transformation products were detected in the water or sediment phases. Mineralization of fluopyram was low, with max 1.8 % AR as CO_2 after 90 days. Non-extractable residues reached a maximum of 8.4 % AR.

An anaerobic water/sediment study also showed a rapid dissipation of fluopyram from water to sediment. Fluopyram did not degrade under anaerobic aquatic conditions. No transformation products were detected. The dissipation rate of fluopyram from water was high, DT50 4.5 days, DT90 84 days. In the total system, the DT50 and DT90 values were greater than 1000 days. Mineralization of fluopyram was minimal, with 0.1 % AR as CO_2 by the end of the study period. Non-extractable residues accounted for 6.1 % AR after 121 days.

3.5.1.4 *Fate in air*

Fluopyram does not absorb light at environmentally relevant wavelengths (>290 nm) and is not expected to undergo direct photolysis. The half-life of fluopyram in air was assessed using the Atkinson model (v. 1.91). A DT50 of 21 hours was estimated (assumes 12 hours day and $1.5 \cdot 10^6$ OH^-/cm^3). Fluopyram is not expected to partition to the atmosphere due to the low Henry's Law constant and subsequently is not expected to be subjected to long range atmospheric transport.

3.5.2 EXPOSURE

3.5.2.1 *Soil*

The predicted environmental concentration of fluopyram in soil (PECsoil) was calculated by Mattilsynet with the Finnish PECsoil calculator, using the worst case application regime (crop: lettuce, 2x250 g a.i/ha/year, application interval 7 days, interception 25%/40%). Since none of the field studies can be considered as relevant for Norwegian conditions, PECsoil should be calculated by using the worst case SFO DT50 lab value, which is 276 days (normalised geo. mean of the pyridyl and phenyl labels from the Laacherhof AXXa soil). This resulted in an initial PECsoil of 0.45 mg/kg and a PECsoil max of 2.09 mg/kg. The plateau level (background concentration) established during the 20 years run in the calculator seems to be at about 1.5-1.6 mg/kg. Based on these calculations, no accumulation in soil is expected.

3.5.2.2 *Groundwater*

For exposure assessment in groundwater both fluopyram and the 7-hydroxy metabolite were evaluated. The 7-hydroxy metabolite was included in the EU evaluation as part of a precautionary approach. In addition to the EU FOCUS scenarios (modelled with PEARL/PELMO) MACRO modelling with Swedish scenarios was performed by Mattilsynet according to the Norwegian GAP. The EU FOCUS scenarios indicated that fluopyram was not expected to leach to groundwater in concentrations >0.1 µg/L. The highest fluopyram value and fluopyram-7-hydroxy values of 0.05 µg/L and 0.02 µg/L, respectively, were found for the apple Piacenza scenario. However, results from modelling with MACROinFOCUS 5.5.3 and Swedish scenarios indicate that both fluopyram and the metabolite fluopyram-7-hydroxy have the potential to exceed 0.1 µg/L in groundwater for all crops, except peas.

3.5.2.3 *Surface water*

Models developed by EU's working group FOCUS estimate predicted environmental concentrations in surface water and sediment for different scenarios. PECsw has been calculated up to Step 3 for all crops by the notifier and Mattilsynet. Step 4 calculations with spray drift mitigation (up to 30 m) and/or run-off mitigation (10-12 m) were performed by Mattilsynet using the Surface Water Assessment Enabler (SWAN) tool.

Max PECsw values for Step 3 calculations of pome fruit (4x100 g/ha), peas (2x250 g/ha) and strawberries (1x300 g/ha) were 2.6, 5.0 and 5.3 µg/kg, respectively (max PECsed: 10.0, 10.5 and 11.2 µg/kg, respectively).

Max PECsw in lettuce at Step 3 was 11.0 µg/L (max PECsed: 12.9 µg/L). As run-off was the main route of entry for the worst case scenario, drift buffers did not reduce the PECsw in Step 3. The introduction of a run-off buffer (10-12m) resulted in a max PECsw of 6.4 µg/L (max PECsed: 12.8 µg/kg).

Max PECsw in beans and strawberries at Step 3 was 15.7 µg/L (max PECsed: 40.6 µg/L). As drainage was the main route of entry for the worst case scenario, drift buffers and run-off buffers did not reduce the PECsw in Step 3. The PECsw and PECsed concentrations obtained in the worst case Step 3 scenario were higher than the concentrations obtained in the Step 2 calculations (PECsw:10.2 µg/L and PECsed: 28 µg/kg).

3.5.3 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.

3.5.3.1 *Mammals*

Fluopyram has low acute toxicity (LD50: >2000 mg/kg bw/d) to mammals. TER_{acute} for the indicator species in orchards, strawberry, leafy vegetables/pulses are estimated as 86, 49 and 42, respectively. These values do not fall below the trigger (<10). The NOAEL from a two-generation reproduction study is 14.5 mg/kg bw/d.

In the first tier risk assessment for orchards, all estimated $TER_{chronic}$ values are above the trigger (<5) for the relevant generic focal species. In the first tier risk assessment, the $TER_{chronic}$ values for the generic focal species 'small herbivorous mammal - vole' are estimated to be 3.2 for strawberry, leafy vegetables, and pulses. This value falls below the trigger, thus prompting a higher tier assessment. However, ecotox colleagues have in the

Northern zone Guidance Document decided that the vole species is not considered relevant for these crops in the Northern zone.

3.5.3.2 *Birds*

Fluopyram has low acute toxicity (LD50: >2000 mg/kg bw/d) to birds. TER_{acute} for the indicator species in orchards and strawberry/leafy vegetables/pulses are estimated as 251 and 36, respectively. These values do not fall below the trigger (<10). There are two long-term endpoints; the NOEC for reproduction (4.5 mg/kg bw/d) is used in the first tier risk assessment and a population-relevant NOAEL (7.2 mg/kg bw/d) is used in the refined risk assessment.

In the first tier risk assessment for orchards, the $TER_{chronic}$ value for the generic focal species 'small insectivorous bird – tit' is estimated to be 2.2 which fall below the trigger and thus prompting a higher tier assessment. In the higher tier risk assessment, $TER_{chronic}$ are estimated to be 6.5 and 6.1 for the focal species blue tit and chaffinch, respectively. These values do not fall below the trigger (<5).

In the first tier risk assessment for strawberries, the $TER_{chronic}$ values for the generic focal species are estimated to be 2.2, 1.6, and 4.8 which fall below the trigger. In the higher tier risk assessment, $TER_{chronic}$ are estimated to be 5.7 and 5.8 for the focal species skylark and starling, respectively. These values do not fall below the trigger (<5). In the higher tier risk assessment, the refined $TER_{chronic}$ value for the white wagtail is estimated to be 2.7, which is below the trigger (<5).

In the first tier risk assessment for leafy vegetables, the $TER_{chronic}$ values are below the trigger values for all the relevant generic focal species, thus triggering a higher tier assessment. In the higher tier risk assessment, the refined $TER_{chronic}$ values for the focal species skylark, white wagtail, and linnet are estimated to be 1.4, 3.3, and 2.1, respectively. These values are below the trigger (<5).

In the first tier risk assessment for pulses, the $TER_{chronic}$ values for the generic focal species 'small insectivorous bird – wagtail' is estimated to be 2.2 which fall below the trigger and thus prompting a higher tier assessment. In the higher tier risk assessment, the refined $TER_{chronic}$ value for the white wagtail is estimated to be 3.3, which is below the trigger (<5).

3.5.3.3 *Bees*

Fluopyram has low contact (LD50: >100 µg a.s./bee) and oral (LD50: >102 µg a.s./bee) toxicity to bees.

Hazard quotients for contact (Qhc) and oral exposure (Qho) are estimated to be <3.0 and <2.9, respectively. None of the hazard quotients exceed the trigger value (>50).

3.5.3.4 *Non-target arthropods*

In Tier 1 laboratory acute contact toxicity studies, formulations with 500 g fluopyram/L showed negligible effects on predatory mites and parasitoids. An extended lab study with the soil dwelling rove beetle did not show effects above the trigger effect level of 50 %. The LR50 is estimated to be > 2000mL product/ha which is more than 3 times the highest application rate.

3.5.3.5 *Earthworms*

Fluopyram has low acute toxicity (LC50: 1000 mg a.s./kg d.w. soil) to earthworms. TER_{acute} is estimated to be 478. This value does not exceed the trigger (<10). In a chronic toxicity test, the NOEC is estimated to be 5620 mL product/ha which is 9 x the highest application rate.

3.5.3.6 *Other soil macro organisms*

Since the soil DT90 for fluopyram is >365 days, the toxicity of Luna Privilege has been tested on the springtail. Fluopyram has low chronic toxicity to *Folsomia candida* (NOEC:104 mg a.s./kg d.w. soil). TER is estimated to be 108, which is not below the trigger (<5).

3.5.3.7 *Litter bag*

A study on the effects on soil litter degradation showed no significant differences in litter mass loss between control (76 %) and treatment groups (77%) after 6 months.

3.5.4 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. A tiered approach is applied. Step 3 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 >100 and >10, respectively.

3.5.4.1 *Fish*

Fluopyram is acutely toxic to fish (96h LC50: >0.98 mg a.s./L) and has moderate chronic toxicity (33 d NOEC: 0.135 mg a.s./L). Luna Privilege has low acute toxic to rainbow trout (96h LC50: >120 mg/L).

Acute TER calculations for fluopyram pass the EU trigger based on Step 3 FOCUS surface water scenarios for pome fruit, peas, and strawberries (single application). Based on Step 4 calculations, which includes 10 m drift buffer + 10-12 m run-off buffer, the acute TER pass the trigger for scenarios in lettuce. The acute TER (>62) for beans/strawberries fail the trigger.

The long-term TER calculations for fluopyram pass the EU trigger based on Step 3 FOCUS surface water scenarios for all crops other than beans/strawberries (TER is 9).

3.5.4.2 *Invertebrates*

Fluopyram has moderate acute toxicity (48h EC50: >0.5 mg a.s./L) and low chronic toxicity (21 d NOEC: 1.22 mg a.s./L) to aquatic invertebrates. Luna Privilege has low acute toxicity to Daphnia (48h EC50: >100 mg/L).

Acute TER calculations for fluopyram pass the EU trigger based on Step 3 FOCUS surface water scenarios for pome fruit and peas. Based on Step 4 calculations, which includes 10 m drift buffer + 10-12 m run-off buffer, the acute TER (>78) fail the trigger for scenarios in lettuce. Acute TER for strawberries (single applications) (>94) and beans/strawberries (>32) fail the trigger.

The long-term TER calculations for fluopyram pass the EU trigger based on Step 3 FOCUS surface water scenarios for all crops.

3.5.4.3 *Sediment dwelling organisms*

Fluopyram has low chronic toxicity to Chironomus riparius larvae (28 d NOEC: 1.4 mg a.s./L (spiked water)).

All TER calculations for fluopyram pass the EU trigger based on Step 3 FOCUS surface water scenarios.

3.5.4.4 *Aquatic plants*

Fluopyram is toxic to duckweed (14d EC50: 2.3 mg a.s./L). Luna Privilege is toxic to duckweed (14d EC50: 6.8 mg a.s./L).

TER calculations for fluopyram pass the EU triggers based on Step 3 calculations.

3.5.4.5 *Algae*

Fluopyram and Fluopyram-lactam are toxic to algae (72 h EC50:>1.1-9.4 mg a.s./L). Luna Privilege has moderate toxicity to algae (72h EC50: 16.1 mg/L).

All TER calculations for fluopyram pass the EU trigger based on Step 3 FOCUS surface water scenarios.

3.5.4.6 *Microorganisms*

No information.

3.5.4.7 *Microcosm/Mesocosm studies*

No information.

3.5.4.8 *Bioaccumulation*

Fluopyram has a low potential for bioaccumulation. The fish bioaccumulation study with bluegill sunfish indicated a low bioconcentration factor (whole fish = 18) and a very rapid clearance half life (1.8 to 3.4 days).

3.6 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

The Panel on Plant Protection Products of the Norwegian Scientific Committee for Food Safety (VKM) has reviewed the documentation and recognised the following properties of the active ingredient fluopyram:

Toxicokinetics
Fluopyram is rapidly and completely absorbed following oral administration, and is readily systemically bioavailable. The highest residue levels are found in liver, kidneys and the Harderian gland, and to a lesser extent in erythrocytes, adrenals, thyroid and ovaries. Log POW value of 3.3 may suggest a potential for bioaccumulation. Several metabolites including fluopyram-7-hydroxy are observed. 90 – 100 % of radioactively labeled fluopyram is excreted via feces and urine 72 - 168 h after oral administration, depending on the type of radioactive label used. Exhalation was negligible.

Toxicity
Fluopyram has low acute toxicity after oral, dermal and inhalation exposure, and is not considered to be a skin- or eye irritant, nor a skin sensitizer.

All *in vitro* and *in vivo* genotoxicity studies are negative.

Body weight and food consumption are affected in feeding studies at the highest dose. Palatability problems are noted in dogs. Liver is the main target organ in all species tested, observed by dose-related increase in organ weight, alterations of clinical parameters and histopathological findings such as hypertrophy or vacuolation. In addition, induction of microsomal liver enzymes is reported in rats at the two highest dose levels.

Pathological changes in kidneys (organ weight increase and hyaline droplet nephropathy) is observed in rats. It has been assumed that the kidney effects are linked to accumulation of α2μ-globulin in the proximal tubules, a rat-specific mechanism of low relevance to humans. The thyroid changes (higher organ weight and follicular cell hypertrophy) in rats has been shown to be accompanied by changes in TSH, T3 and occasionally also T4 levels. Adrenal glands were affected in mice at the highest dose levels.

Decreased thymus and spleen weights in dogs have been observed, and thus immunotoxic effects of fluopyram can not be excluded.

Carcinogenicity
A statistically significant increase in male rat mortality with no clear underlying mechanism has been reported. Liver toxicity with increased organ weight at the higher dosages is accompanied by neoplastic changes. The incidence of liver cell tumours (carcinoma and adenoma) is significantly increased in females receiving 1500 ppm (equivalent to 89 mg/kg bw/day). The total number of benign and malignant liver tumours in female rats was 11 (including 3 animals with carcinoma) as compared to 2 in each of the control, low and mid dose groups.

Dietary administration of fluopyram to the C57BL/6J mouse results in increased incidence of follicular cell adenoma in the thyroid gland.

Reproductive toxicity
In two-generation reproduction study in rats, no reproductive findings is observed up to the highest dose tested. Effects on pup body weight and body weight gain and some other effects observed at the highest dose level of 1200 ppm could be considered secondary to maternal toxicity.

In a rat developmental toxicity study, a dose-related increase in liver weight is noted in the majority of dams. Hepatomegaly was noted in 4 females at the top dose level, and NOAEL for maternal toxicity is set to 30 mg/kg bw/day. An increased incidence of visceral ('thymic remnant present' and 'ureter convoluted and/or dilated'), and skeletal variations ('at least one thoracic centrum split/split cartilage' and 'at least one thoracic centrum dumbbell and/or bipartite/normal cartilage') was reported. 30 mg/kg bw/day was considered as the fetal NOAEL.

In the developmental toxicity study in rabbits, mean body weight gain and food consumption and mean fetal body weight are reduced at 75 mg/kg bw/day, and the incidence of very small fetuses (classified as 'runts') is increased. At this dose, two fetuses from separate litters with the malformation 'gall bladder absent', compared to no instance in the current control group is reported. Thus, the middle dose level of 25 mg/kg bw/day was considered NOAEL for both maternal and developmental toxicity.

Mechanisms and special studies
Decreased motor and locomotor activity, urine stain, and decreased body temperature is reported in acute neurotoxicity studies in rats. 50 mg/kg bw is considered the NOAEL for female rats. No evidence of neurotoxicity is observed at any treatment dose in the 90-day neurotoxicity study in rats.

Mechanistic studies have been conducted to assess the mechanism underlying tumour formation in rat liver and mouse thyroid. Based on these studies, the EU RMS concluded that the tumours in the thyroid of male mice should be considered as non-relevant to humans, while the tumours seen in the liver of female rats should be considered relevant to humans. US EPA and PMRA in Canada found the results of the mechanistic studies insufficient to support the proposed species-specific mode of action for both the liver tumours in female rats, and the thyroid follicular cell tumors in male mice, thus considering both tumour types as relevant to humans.

In the terms of reference VKM has been requested to consider the possible health risk for operators related to the properties of the active substance fluopyram in Luna Privilege, and in particular to evaluate the potential for bioaccumulation, reproductive and neurotoxic effects, discuss possible mechanisms involved in liver and thyroid tumor formation observed in rats, and the establishment of NOAELs and reference values (ADI, AOEL and ARfD).

The following specific points were discussed by VKMs Panel for Plant Protection Products:

4.1.1 THE POTENTIAL FOR BIOACCUMULATION BASED ON THE LONG HALF LIFE (73 H) OF PYRIDYL-LABELED FLUOPYRAM IN FEMALE RATS

The pharmacokinetics and metabolism of fluopyram were studied in rats using phenyl- and pyridyl-labelled substance. Absorption following oral exposure was virtually complete and was followed by systemic distribution. The highest levels of residues were found in liver, and kidneys. The excretion studies showed half-lives in male rats of about 20 and 16 hours for the phenyl- and pyridyl-tagged substance, respectively, while the values for female rats were about 36 and 18 hours (estimated from the cumulative excretion studies). The excretion was

nearly complete after 72 hours. An especially long half life (73 hours) was observed for the terminal elimination of a single low dose of the pyridyl-labelled substance. For the initial elimination phase, the half-life of the compound was however only 10 hours. Thus, this long half-life of the terminal phase in this study is not sufficient to suggest that fluopyram bioaccumulate.

Altogether, the data presented for the substance fluopyram with the relatively high Log POW of 3.3 do not suggest a prominent ability to bioaccumulate. The slightly longer retention time observed for female rats using the phenyl-tagged substance is not sufficient to suggest a sex-specific difference since this difference is not observed for pyridyl labelled fluopyram. Some of the observed differences in the toxicokinetic data may depend on the radiolabeled tag used.

Conclusion: VKM considers the active ingredient fluopyram to have low potential for bioaccumulation. The data do not suggest a sex-specific excretion.

4.1.2 THE NECESSITY OF ADDITIONAL IN VIVO STUDY TO INVESTIGATE ORGAN SPECIFIC GENOTOXICITY DUE TO THE ONCOGENIC EFFECT OBSERVED IN THE RAT AND MOUSE STUDIES.

In the rat carcinogenicity study, a statistically significant increase in mortality was observed in males at 750 and 375 ppm. No cause was found for this. At 750/375 ppm in males and 1500 ppm in females, body weights were reduced. The main target organs were the liver, kidneys and the thyroid gland. Increased liver weights were observed at the highest exposure dose, accompanied by neoplastic alterations. The incidence of liver cell tumours (carcinoma and adenoma) was increased in female rats exposed to 1500 ppm (89 mg/kg bw/day). Combined benign and malign liver tumours in female rats was 11 (including 3 carcinomas), compared to 2 (both benign) in the control group, 2 (both benign) in the low dose group, and 2 (both carcinoma) in the middle dose group.

The mouse carcinogenicity study showed liver, kidneys and thyroid as target organs. An increased incidence of thyroid adenomas was observed in the 750 ppm (105 mg/kg bw/day) dose group. Benign histological changes in the liver (male and female mice) and thyroid gland (male) were also observed in the middle dose group (150 ppm).

Tests for genotoxicity were all negative, both *in vitro* and *in vivo*. I spite of this, the existence of an organ specific genotoxic effect cannot be excluded. Therefore, based on the observed oncogenic effects in rats, the supplementary findings in the mouse studies, and the lack of a likely mechanism for the tumor induction, it should be considered to perform an organ specific genotoxicity assay in rat liver, such as an *in vivo* Comet assay.

Conclusion: It is the opinion of VKM that an *in vivo* Comet Assay in rat liver could be performed to further elucidate the possible genotoxic potential of fluopyram.

4.1.3 ESTABLISHMENT OF THE NOAEL FOR THE 90-DAY FEEDING STUDY IN RATS AND THE REFERENCE VALUE (AOEL)

Body weight and food consumption in rats were affected in nearly all feeding studies at higher dosages. Palatability problems were noted in dogs. Liver was observed to be the main target organ in the species tested; mice, rats and dogs.

The observed liver effects were increased organ weight, altered blood parameters, histopathological alterations (vacuolation and hypertrophy) and induction of microsomal enzymes (P-450, BROD and PROD). Liver effects in rats were observed after oral exposure,

but also following dermal administration of the highest dose (1000 mg/kg bw/day). Changes in red blood cell parameters, prothrombin level and platelet counts were also observed.

Pathological kidney changes (organ weight increase with hyaline droplets) were found predominantly in male rats and associated with accumulation of α2μ-globulin. This is considered as a mechanism that is rat-specific and of less relevance to humans.

The thyroid changes in rats (increased organ weight with follicular cell hypertrophy) were associated with increased TSH, but without a consistent decrease in T3 and T4 levels. Thus it cannot be readily concluded that thyroid alterations are irrelevant to humans. In addition, follicular cell hypertrophy was also observed in the one-year study in dogs.

Most of the findings in rats were at the two highest dosages, 1000 and 3200 ppm. Increased liver weights and/or hypertrophy were also seen at 200 ppm for both male and female animals. Although the number of animals with affected liver is low in the 200 ppm dose group, it represents the starting effective dose of a dose dependent response. Thus, it is the view of VKM that 50 ppm (3.06 mg/kg bw/day) should be used as the NOAEL value for the 90 day feeding study in rats. This view is supported by the observations of 200 ppm also being an affected dosage in the dose dependent alterations of the levels of bilirubin, gamma-glutamyl transferase and cholesterol in female rats.

Conclusion: It is the opinion of VKM that the NOAEL for the 90-day feeding study in rats should be set to 3.06 mg/kg bw/day, resulting in an AOEL of 0.03 mg/kg bw/day.

4.1.4 A HIGHER INCIDENCE OF THE VARIATIONS "AT LEAST ONE THORACIC CENTRUM: SPLIT/SPLIT CARTILAGE AND "AT LEAST ONE THORACIC CENTRUM: DUMBBELL AND/OR BIPARTITE/NORMAL CARTILAGE OBSERVED IN THE RAT DEVELOPMENTAL TOXICITY STUDY, AND IF THESE ARE CONSIDERED TO BE MALFORMATIONS

Developmental toxicity was observed in rats at the high dose level (450 mg/kg bw/day), evident as lower fetal body weight, and increased incidence of two visceral and two skeletal minor variations, outside the in-house historical control values.

Regarding one of the skeletal findings, the "dumb-bell or incomplete ossification and/or bipartite/normal cartilage", it has in a harmonisation workshop on terminology and classification of foetal abnormalities been distinguished between "dumb-bell" and "dumb-bell ossification", with the former being considered as a malformation and the latter as a variation (Solecki et al., 2001).

Therefore, the increase in one of the skeletal findings, considered as a malformation, should be regarded as treatment related. The increased incidence of the other variation was also considered treatment-related. Both the maternal and fetal NOAEL were considered to be 30 mg/kg bw/day.

Conclusion: It is the opinion of VKM that the "dumb-bell or incomplete ossification and/or bipartite/normal cartilage" should be considered as a malformation and regarded as treatment related.

4.1.5 THE MALFORMATION "GALL BLADDER ABSENT" OBSERVED IN THE RABBIT DEVELOPMENTAL TOXICITY STUDY – IS THIS TREATMENT RELATED?

In the rabbit developmental toxicity study, visceral observations included "gall bladder absent" in two foetuses from two litters in the high dose group (75 mg/kg bw/day), compared to no instances in the control group. At this dose level there was also an increase in "runt"

foetuses or small foetuses. The mean percentage of foetuses classified as small was 12.5%, and the percentage of litters affected was 47.6%, compared to 3.0% and 23.8%, respectively, in the control group. The maternal toxicity reported in the high dose group included reduced body weight gain, as well as reduced corrected body weight, however not statistically significant. Since the incidences of the "gall bladder absent" was reported in two different litters, and is not considered to be related to maternal toxicity, the effect should be considered as treatment related.

Conclusion: It is the opinion of VKM that it cannot be excluded that the reported incidence of "gall bladder absent" is treatment related.

4.1.6 IN THE ACUTE NEUROTOXICITY STUDY, FOB AND MOTOR ACTIVITY MEASUREMENTS WERE PERFORMED ON FOUR OCCASIONS: ONE WEEK PRIOR TO TREATMENT, APPROXIMATELY 1 HOUR, 7 DAYS AND 14 DAYS FOLLOWING TREATMENT. HOWEVER, THE TOXICOKINETIC STUDIES HAVE SHOWN THAT TMAX FOR HIGH DOSE WAS 35 H IN MALES AND 42 H IN FEMALES. WERE THESE TIME POINTS FOR THE MEASUREMENTS OPTIMAL IN THIS STUDY?

In the reported neurotoxicity studies, no measurements are given between 1 hour and 7 days following start of exposure. It seems reasonable that measurements should also have been carried out at for instance 8 hours and/or 24 hours. The maximum concentration for many organs, including brain, was reached already 1 hour following oral gavage administration. It can however not be excluded that symptoms may occur and disappear in the relatively long time window between 1 hour and 7 days, and thus be missed in the reported experiment.

Conclusion: It is the opinion of VKM that the time points used for neurotoxic measurements are not optimal to detect neurotoxic effects from acute exposure, since the time window between the first and second measurements is too long.

4.1.7 THE PHENOBARBITAL MECHANISM OF ACTION PROPOSED FOR THE TUMOURS SEEN IN THE LIVER OF FEMALE RATS AND IF THIS IS SUFFICIENTLY SUPPORTED BY THE SUBMITTED MECHANISTIC STUDIES

Several studies were performed to characterize the mechanism underlying tumour formation in female rat liver. Effects of the exposure to fluopyram were compared to that of exposure to phenobarbital. The idea behind this is that phenobarbital has been found to induce liver tumors in rodents while no carcinogenic effects have been observed in humans in spite of its long lasting and extensive use as a pharmaceutical drug. Such a comparison is however generally questionable as a way to exclude a tumor inducing substance from being relevant to humans due to the complexity and lack of complete understanding of the cancer causing mechanisms. In this case, it is also clear that fluopyram and phenobarbital show different effects on several of the parameters studied.

Conclusion: It is the opinion of VKM that the studies where effects of fluopyram and phenobarbital are compared can not be used to exclude human relevance of the tumor-inducing effect of fluopyram in the liver of female rats.

4.1.8 THE MECHANISM OF ACTION PROPOSED FOR THE THYROID TUMOURS SEEN IN THE MALE MICE AND IF THIS IS SUFFICIENTLY SUPPORTED BY THE SUBMITTED MECHANISTIC STUDIES

Studies were performed to assess the mechanism underlying the formation of tumors in the thyroid of male mice. It is often argued that a rodent-specific mode of action for thyroid effects is based on reduced plasma/serum levels of T3 and T4 via the induction of microsomal liver enzymes, resulting in a feedback mechanism that causes increased TSH production with the resulting stimulation and proliferation of the thyroid. As for the comparison with phenobarbital effects in relation to liver tumors in female rats, this is a challenging procedure. Increase in TSH may occur via different mechanisms in different species, also in situations where T3 and T4 are observed to be reduced. In the present studies, increased thyroid weight and follicular cell hypertrophy in exposed rats were often associated with increased TSH, but less consistent with a decrease in T3 and T4 levels. In some instances, also increases in T3 and T4 were observed. An increase in TSH and a decrease in T3 and T4 were observed in the mechanistic studies on male mice. The activity of UDPGT in the liver was however not induced. Thus, there are several reasons to conclude that although the human relevance can not be proven, the experiments performed are not sufficient to conclude that the finding of thyroid tumors in male mice are of no relevance to humans. This view is also supported by the finding of thyroid follicular epithelial hypertrophy in the one-year study in male dogs.

Conclusion: VKM found the results from the mechanistic studies insufficient to support the proposed mode of action for the induction of thyroid follicular cell tumors in male mice. The main deficiency included lack of dose-response concordance between key precursor events and tumor incidence. It is therefore the opinion of VKM that the mechanism underlying the induction of thyroid tumors in male mice could be relevant for humans.

4.1.9 GENOTOXICITY AS A MECHANISM OF ACTION FOR THE TUMOURS OBSERVED IN THE LIVER AND THYROID

There is no indication of genotoxicity being a mechanism for the formation of thyroid tumors. However, genotoxicity cannot be excluded as a mechanism of action for the liver tumors, and *in vivo* comet assay in rat liver is suggested to further elucidate this possibility. The rationale has been discussed in 4.1.2. and 4.1.8.

4.1.10 ESTABLISHMENT OF REFERENCE VALUES

NOAEL values:
VKM proposes a NOAEL of 1.2 mg/kg bw/day for setting of ADI based on the 2 year chronic toxicity study in rat, and is of the opinion that the test substance-related increased incidences of neoplastic findings in the liver, kidney and thyroid gland, is considered relevant for humans.

VKM proposes a NOAEL of 3.06 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 liver weight and/or hypertrophy is considered relevant for humans.

VKM proposes a NOAEL of 25 mg/kg bw/day for setting ARfD based on a developmental toxicity study in rabbits, and is of the opinion that the test substance-related reduced foetal weight and “gall bladder absent” is considered relevant for humans.

ADI
An ADI of 0.012 mg/kg bw/day is proposed for fluopyram based on applying a 100-fold uncertainty factor to NOAEL of 1.2 mg /kg bw/day from a 2 year feeding study in rats. The uncertainty factor accounts for interspecies extrapolation (10X) and intraspecies variability (10X).

AOEL
An AOEL of 0.03 mg/kg bw/day is proposed for fluopyram based on applying a 100-fold uncertainty factor to the NOAEL of 3.06 mg /kg bw/day determined in the 90-day feeding study in rats. The NOAEL is based on increased liver weight and hypertrophy.

AR_fD
An AR_fD of 0.25 mg/kg bw/day is proposed for fluopyram, based on applying a 100-fold uncertainty factor to the NOAEL of 25 mg/kg bw/day determined in the developmental toxicity study in rabbits.

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 in section 4.1.

4.2.1.1 *Operator, worker and bystander exposure*

Operator exposure:
The AOEL for field use of fluopyram is slightly exceeded without the use of personal protective equipment (PPE) (107 % for UK POEM and 123% for German model). The use of gloves decreases the estimated exposure to below the AOEL (83 % for UK POEM and 67% for German model).

The AOEL for greenhouse use of fluopyram is not exceeded, even without protective equipment.

Re-entry and bystander exposure:
Re-entry and 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 is 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, in particular the potential for groundwater contamination, safety zones and possible effects on birds and aquatic organisms. The Panel on Plant Protection Products of the Norwegian Scientific Committee for Food Safety (VKM) has reviewed the documentation and points out the following inherent properties of the active substance and possible metabolites:

Degradation/mobility

Fluopyram is stable in water under acidic, neutral and alkaline conditions. The total dissipation rate in water-sediment systems is low, and no major transformation products are detected in the water or sediment phases. Rapid dissipation of fluopyram from water to sediment is observed.

In soil, Fluopyram is metabolized to fluopyram-7-hydroxy which is further cleaved to pyridyl-carboxylic acid and benzamide. The pyridyl-carboxylic acid is transformed to methyl-sulfoxide and microbial breakdown of the phenyl ring finally results in CO2.

Degradation of fluopyram is moderate to low with DT50 of 162-746 days (geometric mean 290 days). DT50 values are longer than the study duration in all soils, resulting in uncertain DT values. Degradation of the metabolite fluopyram-7-hydroxy is medium to high with DT50 of 5.8-18 days (geometric mean 11 days).

Bound residues were 15% and mineralisation to CO2 27 %. Fluopyram is stable under anaerobic conditions in soil, and photolysis is not of significant importance as a route of transformation. Field dissipation is investigated at six sites in European soil, three of which (Germany, UK and Sweden) could be considered relevant for parts of Norway. DT50 values show moderate rates of dissipation, DT50 145-179 days (geometric mean 162 days). The DT90 values were > 1000 days in all the North European studies, and no residues were detected below 30 cm.

Soil adsorption of fluopyram is medium and that of the metabolite fluopyram-7-hydroxy moderate to medium. Koc(des) and Koc(ads) values for fluopyram-7-hydroxy is suggested to show a strengthened binding once adsorbed to the soil (irreversible binding).

The following specific points were discussed:

4.3.1 DEGRADATION AND ACCUMULATION IN SOIL. THE RELEVANCE OF THE FIELD STUDY CONDUCTED IN STAFFANSTORP, SWEDEN, FOR NORWEGIAN CONDITIONS. IS IT ACCEPTABLE TO USE THE RESULTS (DT50) FROM THIS STUDY TO CALCULATE PECSOIL?

Staffanstorp is located in southern Sweden. The soil has an organic carbon content of 1.4 %, a pH of 7.3 and a yearly average temperature and rainfall of 9.3 deg C and 700 mm, respectively. These values are within the wide range of conditions found Norway, but do not necessarily represent conditions relevant to calculate the exposure representative for a significant number of Norwegian agricultural sites. VKM therefore recommends that degradation rates obtained from laboratory studies (worst case SFO DT50) should be used in models for calculation of PEC values for fluopyram.

Conclusion: It is the opinion of VKM that worst case degradation rates from laboratory studies should preferably be used to calculate PECsoil values for fluopyram.

4.3.2 THE POTENTIAL FOR GROUNDWATER CONTAMINATION FOR BOTH FLUOPYRAM AND FLUOPYRAM-7-HYDROXY.

Exposure concentrations calculated for groundwater with the MACRO model exceed 0.1 ug/L for both fluopyram and fluopyram-7-hydroxy for several Swedish and one Norwegian

scenario. VKM considers these calculations to be valid and relevant, and that contamination of groundwater may occur as a result of Luna Privilege usage.

Conclusion: It is the view of VKM that both fluopyram and fluopyram-7-hydroxy have a high potential for groundwater contamination.

4.3.3 THE RELEVANCE OF USING A RUN-OFF BUFFER AS A MITIGATION MEASURE IN STEP 4. THE VALUES USED FOR RUN-OFF REDUCTION IN A 10-12 M VEGETATED BUFFER STRIP ARE GIVEN IN IN THE FOCUS GUIDANCE DOCUMENT ON LANDSCAPE AND MITIGATION, VOL. 1 (2007), TABLE 7, P. 33 . CAN THESE VALUES BE CONSIDERED RELEVANT FOR NORWAY?

The model predicting effect of vegetated buffer zones on run-off levels is based on several studies showing a reduction in run-off levels with increased buffer zones (FOCUS landscape and mitigation, 2007). It is the opinion of VKM that the test sites may not be representative for Norwegian agricultural sites in terms of for example slope steepness, and amount/intensity of rainfall. In the FOCUS report it is underlined that the efficacy of buffer zones needs to be considered on a case-by-case basis by Member States. VKM agrees that buffer zones influence run-off levels, but do not support the suggested reduction factors for run-off until they have been validated and considered relevant and representative for Norwegian agricultural sites.

Conclusion: It is the opinion of VKM that efficacy of buffer zones needs to be considered on a case-by-case basis, and that further validation of the model values is necessary.

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 3.5.3-3.5.4 and exposure-, dose/response assessments and risk scale described in section 2.2. In additions documents from EFSA and Draft Assessment Reports (DAR) has been used. The following abilities of the active substance and possible metabolites have been reconized:

Exposure
Environmental predictive concentrations of fluopyram in soil (PECsoil) has been calculated with the Finnish PECsoil calculator to an initial PECsoil of 0.45 mg/kg and a max PECsoil of 0.96 mg/kg over twenty years. Background concentrations reached a plateau of 0.4-0.5 mg/kg and the calculations does not suggest accumulation in soil. The EU FOCUS scenarios suggest that fluopyram should not leach to groundwater in concentrations >0.1 µg/L. Results from modelling with MACROinFOCUS 5.5.3 and Swedish scenarios indicate however that both fluopyram and the metabolite fluopyram-7-hydroxy have the potential to exceed 0.1 µg/L in groundwater. PECsw has been calculated up to Step 3 by the notifier and Mattilsynet, while Step 4 calculations with spray drift and/or run-off mitigation were performed by Mattilsynet using the Surface Water Assessment Enabler (SWAN) tool. PECsw values for Step 3 calculations ranged from 2.6 to15.7 µg/kg for different crops. Drift buffers did not reduce the PECsw in Step 3, while a run-off buffer of 10-12m resulted in a max PECsw of 10.2 µg/L.

Terrestrial organisms
Fluopyram has low acute toxicity to mammals and birds, and the TER_{acute} values are above the trigger value of 10. There are two long-term endpoints; the NOEC for reproduction (4.5 mg/kg bw/d) is used in the first tier risk assessment and a population-relevant NOAEL (7.2

mg/kg bw/d) is used in the refined risk assessment. In the first tier risk assessment for orchards, the $TER_{chronic}$ value for 'small insectivorous bird – tit' is estimated to be 2.2 which is below the trigger and prompting higher tier assessment. In the higher tier assessment, $TER_{chronic}$ are estimated to 6.5 which do not fall below the trigger of 5. In first tier risk assessment for strawberries, the $TER_{chronic}$ values for are estimated to be between 1.6 and 4.8, which is below the trigger value. In higher tier assessment the $TER_{chronic}$ are above the trigger of 5. For leafy vegetables, the $TER_{chronic}$ values are below the trigger values for all the relevant species. In the higher tier assessment, the refined $TER_{chronic}$ values are between 1.4 and 3.3, thus below the trigger of 5. In the first tier assessment for pulses, the $TER_{chronic}$ value for "small insectivorous bird – wagtail' is 2.2 which is below the trigger, and in the higher, the refined $TER_{chronic}$ value is 3.3, also below the trigger of 5. Fluopyram has low contact and oral toxicity to bees; show negligible effects on predatory mites and parasitoids; has low acute toxicity to earthworms; and low chronic toxicity to Folsomia candida.

Aquatic organisms
Fluopyram is acutely toxic and has moderate chronic toxicity to fish. The acute TER calculations pass the EU trigger based on Step 3 and Step 4 calculations except for beans/strawberries. The long-term TER calculations pass the EU trigger based on Step 3 FOCUS surface water scenarios for all crops other than beans/strawberries.

For aquatic invertebrates, fluopyram has moderate acute toxicity and low chronic toxicity. Acute TER for beans/strawberries (>32) fails however the trigger. Fluopyram is toxic to duckweed and algae, but passes the EU triggers based on Step 3 calculations. Fluopyram has a low potential for bioaccumulation.

The following specific points were discussed:

4.4.1 EFFECTS AND RISKS TO TERRESTRIAL ORGANISMS. THE REFINEMENTS USED IN THE RISK ASSESSMENT FOR BIRDS.

The Panel was asked to consider the refinements used in the risk assessment for birds and all the suggested refinements are considered to be relevant. Based on the refined risk calculations, the use of Luna Privilege with the active substance fluopyram with the proposed application scheme in Norway, represents the following risks for adverse effects on birds: Orchards: minimal risk. Strawberries (only open field considered) and pulses: moderate risk. For leafy vegetables in open field: medium risk. Thus, even with all possible refinements included, TER values are below the trigger for all considered crops except for orchards. It is the opinion of VKM that the high level of refinement calls for a higher margin of safety in the risk assessment and therefore considers the risk as medium for strawberries and pulses and high for lettuce in open field.

Conclusion: Even with all possible refinements included, TER values are below the trigger for all considered crops except for orchards. It is the view of VKM that the data indicate medium risk for strawberries and pulses, and high risk for lettuce in open field.

4.4.2 EFFECTS AND RISK TO AQUATIC ORGANISMS. THE TER CALCULATIONS FOR FISH AND AQUATIC INVERTEBRATES, SPECIFICALLY THE CONSEQUENCES OF USING LC50 VALUES BASED ON EITHER NO EFFECT IN THE HIGHEST TESTED CONCENTRATION OR SURROGATE LC50 AS ENDPOINTS IN THE ACUTE ASSESSMENT, ESPECIALLY IN THE CONTEXT OF THE WATER SOLUBILITY; AND THE INCLUSION OF A RUN-OFF BUFFER IN THE STEP 4 PEC

Although the reported solubility of fluopyram in water is 16 mg/L, the aquatic toxicity studies have only included exposure concentrations up to approximately 1 mg/L. This is apparently due to technical problems in the preparation of stable test solutions with higher concentrations. The LC50 from acute toxicity tests on fish and invertebrates are higher than the highest concentration tested (0.98 mg/L and 0.5 mg/L, respectively). Studies with the product do however show LC50 values of > 49.8 mg/L and > 41.5 mg/L for fish and invertebrates, respectively. This indicates that use of the unbound LC50 values from the tests with the active substance in the TER calculations with a TER trigger value of 100 is overly conservative. VKM therefore suggests reducing the acute trigger for both invertebrates and fish from 100 to 10 in TER calculations based on the unbound LC50-values for fluopyram. For acute toxicity, the trigger is then not exceeded for any of the crops.

For chronic toxicity, the scenarios with strawberries and beans give a TER-value exceeding the trigger (value of 9; trigger is ≤ 10). Thus, VKM concludes that there is a moderate risk of chronic effects on fish when Luna Privilege is applied in beans/strawberries without use of a vegetated bufferstrip for reduction of run-off transport.

Conclusion: It is the opinion of VKM that use of the LC50 values from tests with fluopyram in the TER calculations with a TER trigger value of 100 is overly conservative and suggests a reduction of the acute trigger for both invertebrates and fish from 100 to 10 for such calculations. Thus, the trigger for acute toxicity is not exceeded for any of the crops. For chronic toxicity, VKM concludes that there is a moderate risk of effects on fish when Luna Privilege is applied to beans/strawberries without the use of a vegetated mitigation bufferstrip.

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

It is the opinion of VKM that the active ingredient, fluopyram, has low potential for bioaccumulation, and that the data do not suggest a sex-specific excretion.

It is the view of VKM that an *in vivo* Comet Assay in rat liver could be performed to further elucidate the possible genotoxic potential of fluopyram.

Based on the reported data it can not be excluded that the observed incidence of “gall bladder absent” is treatment related.

VKM proposes that NOAEL for the 90-day feeding study in rats should be set to 3.06 mg/kg bw/day, resulting in an AOEL of 0.03 mg/kg bw/day.

VKM considers the “dumb-bell or incomplete ossification and/or bipartite/normal cartilage” as a malformation and that it should be regarded as treatment related.

It is the view of VKM that the time points used for neurotoxic measurements are not optimal to detect neurotoxic effects from acute exposure, since the time window between the first (1 hour) and second (7 days) measurements is too long.

It is the opinion that the studies where effects of fluopyram and phenobarbital are compared can not be used to exclude human relevance of the tumor-inducing effect of fluopyram in the liver of female rats.

Finally, it is the opinion of VKM that the results from the mechanistic studies are insufficient to support the proposed mode of action for the induction of thyroid follicular cell tumors in male mice, and that the observed induction of thyroid tumors in male mice could be relevant to humans.

VKM proposes:

- NOAEL of 1.2 mg/kg bw/day based on a 2 year feeding study in rats.
- ADI: 0.012 mg/kg bw/day
- AOEL: 0.03 mg/kg bw/day
- ARfD: 0.25 mg/kg bw/day

Risk calculations for field use show minimal risk if personal protective equipment is used. The AOEL for greenhouse use of fluopyram is not exceeded, even without protective equipment. Re-entry and bystander exposure is calculated to be well below the AOEL.

5.2 ENVIRONMENT

It is the opinion of VKM that worst case degradation rates from laboratory studies should preferably be used to calculate PECsoil values for fluopyram.

It is the view of VKM that both fluopyram and fluopyram-7-hydraoxy have a high potential for groundwater contamination.

VKM means that the efficacy of buffer zones needs to be considered on a case-by-case basis, and that further validation of the model derived values is necessary.

It is further the opinion of VKM that all the refinements used in the risk assessment for birds are relevant. Since the TER values estimated for all crops except for orchards are below the trigger following refinements, it is the view of VKM that the data indicate medium risk for strawberries and pulses, and high risk for lettuce in open field.

Finally, it is the view of VKM that the use of a TER trigger value of 100 in the TER calculations for aquatic acute toxicity based on unbound LC50 values from tests with fluopyram is overly conservative, and suggests a reduction of the acute trigger for both invertebrates and fish from 100 to 10 for such calculations. Thus, the trigger for acute toxicity is not exceeded for any of the crops. For chronic toxicity, VKM concludes that there is a moderate risk of effects on fish when Luna Privilege is applied to beans/strawberries without the use of a vegetated mitigation buffer-strip.

6 Documentation

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