Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

Risk assessment of the fungicide Talius with the active substances proquinazid

Opinion of the Panel on plant protection products of the Norwegian Scientific Committee for Food Safety

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Summary

Talius is a new fungicide containing the new active substance proquinazid. Talius is a fungicide against cereal powdery mildew (*Blumeria graminis)* in cereals and grass seed. The risk assessment was finalized at a meeting Mai 29, 2012, by VKM's Scientific Panel on plant protection products (VKM). VKM is in particular asked by the Norwegian Food Safety Authority to look at the following:

- The human health risk for operators related to the properties of the active substance and the product.
    - The effects seen in studies on dog and if these effects warrant a classification for chronic toxicity.
    - The oncogenic effects in liver and thyroid.
    - The establishment of reference values (ADI, AOEL and ARfD).
    - Dermal absorption.
    - The classification and labelling of the active substances and the product.
- The fate and behaviour in the environment and the ecotoxical effects and risks with regard to the properties of Talius and proquinazid.

VKM's conclusion is as follows:

Health

VKM concluded that a less serious effect (dose-related ocular discharge increase) was seen in dogs in both the 90 days study and 1 year-study.

The opinion of the Panel is that cholangiocarcinomas is relevant for the classification of cancer and VKM is concerned about these effects.

VKM proposes an NOAEL of 1.2 mg/kg bw/day for proquinazid based on the 2 year study with rats.

VKM support:

- The proposed ADI value of 0.01 mg/kg bw/day.
- The proposed AOEL value of 0.02 mg/kg bw/day.
- The proposed AR_fD value of 0.2 mg/kg bw/day.
- The proposed classification from The Norwegian Food Safety Authority.

VKM supports The Norwegian Food and Safety Authority calculations for dermal absorption under Norwegian directions for use (2.6 times higher dilution).

Environment

Proquinazid can be persistent under prevailing conditions in Norway and the Panel considers the results from the Finnish PEC calculator to be relevant for Norwegian conditions and expects that repeated annual applications may cause accumulation in soil up to an equilibrium level under Norwegian conditions.The potential for groundwater contamination from leaching of proquinazid and its metabolites are low. There are minimal risks for toxic effects of proquinazid to terrestrial organisms, sediment dwelling organisms, aquatic plants, and algae with the proposed application regime.

For fish and invertebrates minimal risks are calculated provided that a 3 m buffer zone is used.

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 20, 2012 for VKM to perform a risk assessment on use of the pesticide Talius containing the active substance proquinazid. The risk assessments of the product were finalized by VKM in June, 2012.

Terms of reference

Talius is a new product containing the new active substance proquinazid. The application is for use against cereal powdery mildew (*Blumeria graminis*) in cereals and grass seed.

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

- The human health risk for operators related to the properties of Talius and proquinazid. The Panel is in particular asked to look at the following:
  - The effects seen in studies on dog and if these effects warrant a classification for chronic toxicity.
  - The oncogenic effects in liver and thyroid.
  - The establishment of NOAELs and reference values (ADI, AOEL and ARfD).
  - Dermal absorption.
  - The classification and labeling of the active substance and the product.
- The fate and behaviour in the environment and the ecotoxicological effects and risks with regard to the properties of Talius and proquinazid.

1 Background documentation

VKM's risk assessment is based on the Norwegian Food Safety Authority's evaluation (2012) of the documentation submitted by the applicant. The Norwegian Food Safety Authority publishes both their evaluation of Talius 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 VKMs 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 for animal to human. Then the limits are compared to the operator exposure and human exposure to possible residues in food.

The UKPoem and the German model estimate of exposure are used to estimate the 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 their assessment on the models whenever exposure data for the product is not presented.

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 case the estimated exposure significantly exceeds AOEL, 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 take into consideration critical co-formulants of the product when the degree of 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 photodegradation, 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 evt. HQ_C is the ratio 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)

Talius is a new product containing the new active substance proquinazid. Proquinazid is approved for use in EU till 31.07.2020. Talius is an emulsifiable concentrate (EC) formulation containing 200 g/L of the active substance. The application is for use against cereal powdery mildew *(Blumeria graminis)* in cereals and grass seed.

Proquinazid is a vapour active, local systemic fungicide with translaminar effects. It should be used preventively and its activity lasts 4 to 6 weeks.

In the Norwegian field studies Talius was compared with Forbel 750 (fenpropimorf) and appeared equally effective. The mode of action of Talius makes it a good mixing partner for *B. graminis* fungicides already in use in Norway and could significantly reduce the risk of resistance development towards products already registered. Forbel 750 is now the only special mildew product on the Norwegian market. There is no indication of negative effects of Talius on beneficial organisms.

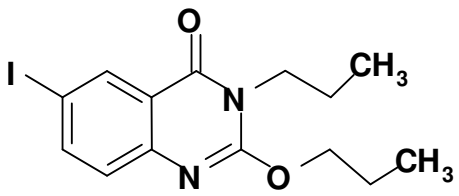
The proposed application rate is 250 mL Talius/ha (50 g proquinazid/ha), , and maximal application number is two per season. Talius should be applied in a volume of 100 to 300 L/ha (10-30 L/daa) of water with a broadcast sprayer using ground directed spraying.

Based on the product's use in cereals and grass seed, the standardized area dose is set to 250 mL Talius/ha (50 g proquinazid/ha) corresponding 25 mL/daa (5 g a.s/daa).

3.1 IDENTITY AND PHYSICAL/CHEMICAL DATA

Product name	Talius
Active substance	proquinazid
Formulation	Emulsion concentrate (EC)
Concentration of active substance	200 g/L
IUPAC-name	6-iodo-2-propoxy-3-propylquinazolin-4(3H)-one
CAS number	189278-12-4

Structural formula



Molecular weight 372.21 g/mol

Solubility in water	Moderate	0.97 mg/L (25°C)
Vapour pressure	Low	9×10^{-5} Pa (25°C)
Henrys law constant	Medium	3×10^{-2} Pa m^3/mol
log Pow	Very high	5.5 (25°C)
pKa	No dissociation	

3.2 TOXIC EFFECTS AND POTENTIAL FOR HUMAN EFFECTS

3.2.1 PROQUINAZID

3.2.1.1 *Toxicokinetics*

Absorption: Proquinazid has absorption of approximately 90%. Males had faster absorption, metabolism and excretion than females. No correction factor for absorption is needed for the setting of AOEL.
Distribution: Proquinazid and its metabolites were widely distributed to all body tissues. The peak plasma concentration time was at 4-8 hours at low dose and 6-10 hours at high dose for single exposure. The highest tissue concentrations besides in GI-tractus, were found in adrenals, liver, kidneys, fat, pituitary and thyroid (and in uterus and ovary in females at high dose). After repeated exposure highest tissue levels were found in liver, kidneys and fat.
Metabolism: Metabolism of proquinazid was extensive. The major metabolic reactions were hydroxylation of the phenyl ring and of the propyl and propxy side chains. The hydroxylated side chains were further oxidised to carboxylic acids and /or hydrolysed prior to being excreted in urine and faeces. There was a minor de-iodination pathway. Repeated exposure led to a decline in glucuronidation before secretion of the metabolite IN-NB673.
Excretion: At both high and low dose levels, 85-88% of the administered dose was excreted within 48 hours (43-56% in urine and 31-43% in faeces after single exposure. After one week, 91-97% was excreted in urine and faeces. Males at the high dose had a more rapid excretion in urine than females. A large proportion was excreted via bile and there was enterohepatic circulation. Repeated exposure leads to more excretion via faeces. The amount of excretion in urine was rather constant. The relative long terminal elimination half-lives that can be calculated, is not reflected in the tissues concentrations measured after repeated exposure. Thus the bioaccumulation potential seems to be of low concern.

3.2.1.2 *Acute toxicity, irritation and sensitisation*

Proquinazid is of low acute toxicity after oral, dermal and inhalation exposure, and therefore no classification is required. Proquinazid was not found to be neither a skin- or eye irritant nor a skin sensitizer.

3.2.1.3 *Genotoxicity*

All *in vitro* and *in vivo* genotoxicity studies were shown to be negative.

3.2.1.4 *Subchronic and chronic toxicity*

The target organs were the liver and thyroid with hepatocellular hypertrophy, thyroid hypertrophy and hormone effects. Ocular discharge was seen in studies on dog.

3.2.1.5 *Carcinogenicity*

Proquinazid was oncogenic, causing thyroid tumours and liver tumours. An increase in TSH and decreases in T3 and/or T4 were observed. It is proposed that proquinazid should be classified as carcinogenic category 3 and assigned the symbol Xn and R40 (Limited evidence for a carcinogenic effect) based on the increased incidence of hepatocellular adenomas in female rats, together with the increased incidence of intestinal- type "cholangiocarcinomas" in female rats. Although there is some uncertainty as to whether "cholangiocarcinomas" should be regarded as tumours, and hepatocellular adenoma in rats are not a strong basis for proposing classification, it is appropriate to be precautionary and propose R40, especially as both types of lesion were increased at a relatively modest dose level (35 mg/kg bw/day).

3.2.1.6 *Reproductive toxicology and teratogenesis*

Proquinazid is not considered toxic to reproduction. Some effects on pup weight were seen at dose levels that also gave maternal effects. Proquinazid is not found teratogenic in rats and rabbits.

3.2.1.7 *Neurotoxicity*

Due to the bad timing of FOB testing day 1 in the acute neurotoxicity study, it is difficult to draw a conclusion regarding neurotoxicity. It cannot be excluded that the neurobehavioral effects seen day 8 in the acute study results from systemic toxicity rather than from a direct neurotoxic effect. The effects are not of a serious category that warrants classification for specific organ toxicity.

3.2.1.8 *Special studies*

Mechanistic investigations during the chronic rat study showed and increase in cytochrome P450 activity and induction UDP glucuronyltransferase in the liver. Thus, the proposed mechanism of induction of proquinazid-induced thyroid hormonal changes is induction of UDP glucuronyltranferase leading to decreased half-life of T4 with a resulting increase in TSH secretion. Inhibition of hepatic 5'-deiodinase, with increased rT3 and decreased T3, also contributes to the increased TSH.

3.2.1.9 *Human data*

No data reported.

3.2.1.10 *Classification and labelling*

The proposed classification is **Xn;** Carc. Cat. 3, R40 (Limited evidence for a carcinogenic effect).

3.2.1.11 *Reference values*

ADI

The ADI is 0.01 mg/kg bw/day based on the NOAEL of 1.2 mg/kg bw/day from the 2-year feeding study in rat. The UF of 100 is applied. (EFSA)

AOEL

The AOEL is 0.02 mg/kg bw/day based the NOAEL of 2 mg/kg bw/day from the 90-day feeding study in rat. The UF of 100 is applied. (EFSA)

ARfD

The AOEL is 0.2 mg/kg bw/day based on ocular discharge in one dog at 19 mg/kg bw/day in the first week of the 90-day study. The UF of 100 is applied. (EFSA)

3.2.1.12 *Metabolites*

IN-MM671, a metabolite not present in the rat metabolism, is of low acute oral toxicity to rats (LD 50 >2000 mg/kg bw) and was not genotoxic in an *in vitro* bacterial gene mutation assay and an *in vivo* mouse bonemarrow micronucleus assay.

3.2.1.13 *Co-formulants*

Talius contains co-formulants that are responsible for the dermal irritation and severe eye irritation of the product.

3.2.2 TALIUS

3.2.2.1 *Acute toxicity*

Talius has low toxicity by inhalation, ingestion and by dermal exposure. Talius is found irritating to skin and may cause serious damage to the eye. The product is not found to be a skin sensitizer.

3.2.2.2 *Classification and labelling*

Talius is classified Xn; R40. Xi; R38-41.

3.2.2.3 *Dermal absorption*

Calculations of dermal absorption *in vivo* in the rat include residues in all tape strips except the two outermost, using data from the end of the study. For the *in vitro* calculations, all tape strips are included as residues in the individual tape strips were not reported. This resulted in a 2-fold absorption of the concentrated product in the rat versus human skin. For the tested dilution, the absorption was approximately the same in rat and human. Dermal absorptions of 3.25 % for the formulated product and of 29.45 % for the diluted product tested are used in the calculation of the operator exposure. Norwegian directions for use give a 2.6 times higher dilution than the dilution tested. Higher dilution can result in a somewhat higher dermal uptake in percentage. Additional calculations has used 75% uptake of the aqueous dilution reflecting Norwegian directions for use.

3.2.2.4 *Operator, worker and bystander exposure*

3.2.2.4.1 Operator exposure

AOEL is exceeded in both models without PPE and is still exceeded when using PPE (gloves) in the UK POEM. However the results of the German model shows that AOEL is not exceeded when using PPE (gloves + coveralls and sturdy footwear under application)

3.2.2.4.2 Re-entry and bystander exposure

Manual activities before harvest in cereals are rare. Worker exposure calculation in grapes with re-entry activities (worst case) gave a value < 1 % of the AOEL.

No calculation for bystander exposure was performed for cereals. Bystander exposure calculations for grapes (worst case) gave a value << 1% of the AOEL

3.2.3 RESIDUES IN EDIBLE PRODUCTS

Not considered in this report.

3.3 ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL EFFECTS

3.3.1 ENVIRONMENTAL FATE AND BEHAVIOUR

3.3.1.1 *Degradation in soil*

During aerobic degradation of proquinazid in soil under laboratory conditions, the main metabolite was IN-MM671 (up to 65% of applied radioactivity (AR). IN-MM671 is dealkylated to IN-MM991 (max 7% AR, >10% in the radiolabelled field study). A minor pathway is the formation of the metabolite IN-MM986 (up to 8% AR; >10% AR in the radiolabelled field study) from proquinazid. The degradation pathway is similar for anaerobic conditions, with IN-MM671 as the main metabolite (up to 45%). No other metabolites were found at levels >5% AR.

The aerobic degradation of proquinazid was medium to low (normalised DT50: 24-239 days, geometric (geo) mean: 60 days). Aerobic degradation of metabolite IN-MM671 was medium to moderate (normalised DT50: 47-156 days, geo mean: 81 days). The degradation of the other two soil metabolites was medium. Mineralization is relatively low, accounting for up to 10% AR at 120-122 days, whilst unextracted radioactivity accounted for up to 15% AR.

At 10°C proquinazid, IN-MM671 and IN-MM991 degrade with a moderate rate (DT50: 79 days, 145 days, 121 days). IN-MM986 has a medium degradation rate (DT50: 38 days).

An anaerobic water/sediment study was provided as a surrogate for an anaerobic soil study. Proquinazid had a moderate degradation rate (DT50: 61 days) in the total system, while IN-MM671 had a low rate of degradation (DT50: 584 days). Mineralization was low. Unextracted radioactivity accounted for 14% AR.

Photolysis may be an important route of degradation for proquinazid in soil as the substance degrades faster when irradiated (DT50:16 days vs. DT50 (dark control): 82 days). The main metabolite was IN-MM671 (14% AR after 7 days of continuous radiation).

Four studies investigating the dissipation of proquinazid in eight different European soil types have been submitted. The field dissipation of proquinazid in soil was medium (DissT50: 5.5 -

70 days, geo mean: 22 days). For the metabolite IN-MM671, the dissipation was moderate to low (DissT50: 29-394 days, geo mean: 153 days). IN-MM986 had a DissT50 ranging from 34-69 days (geo mean: 40 days), having a medium rate of dissipation. IN-MM991 had a medium to moderate dissipation rate (DissT50: 54-104 days, geo mean: 75 days).

Two soil accumulation studies were conducted in northern and southern Europe at application rates relevant for Norway. No residues of proquinazid or any of the metabolites were detected, with the exception of IN-MM671, which was found in the soil sample of one site at a concentration of 0.006 mg/kg.

3.3.1.2 *Sorption/mobility*

The adsorption of proquinazid (Kf: 194, Koc: 12870) and the metabolite IN-MM671 (Kf: 45, Koc: 3279) is very high. The adsorption of IN-MM986 (Kf: 29, Koc: 2376) is high. The adsorption of IN-MM991 (Kf: 3.3, Koc: 264) is medium. All values are arithmetic means. The Koc of IN-MM671 increased with decreasing pH, while the Koc of IN-MM986 seemed to increase with increasing silt and clay content.

3.3.1.3 *Degradation in water*

Both proquinazid and its metabolites IN-MM671, IN-MM986, IN-MM991, and the aqueous photolysis metabolite IN-MT884 were considered to be hydrolytically stable at all pH values tested.

Photolysis may be an important degradation pathway for proquinazid. Major metabolites formed during photolysis were IN-MM671 (20% AR), IN-MM986 (15% AR), and IN-MT884 (31% AR). Theoretical half-lives in the top layer (0.001 cm) of an aquatic system calculated by integrating the half-lives over a full day in summer were <1 hour (proquinazid), 16.1 days (IN-MM671), 32.8 days (IN-MM986), 12.7 days (IN-MM991) and 132 days (IN-MT884). Due to bad fitting practice when calculating the DT50 of IN-MM991 and the low amount of data points from maximum formation of IN-MT884, DT50 values for these two metabolites are not considered reliable by the RMS.

Proquinazid is not readily biodegradable.

In a study with two water/sediment systems a rapid partitioning of proquinazid to the sediment was observed (DissT50water <1 day). The DT50 of proquinazid in the total system indicated moderate to high persistence (DT50: 36-136 days). The principal degradate in the sediment phase was IN-MM671 (up to 68% AR). IN-MM671 seems to be strongly absorbed to the sediment. No decline phase was observed for IN-MM671 during the study period, and hence no accurate DT50 could be determined. However, EFSA concludes that IN-MM671 is very highly persistent in both systems (DT50 > 500 days). The mineralization rate was very low (CO_2 0.2-1.4% AR after 100 days). Unextracted residues bound to soil organic matter accounted for up to 15% AR.

3.3.1.4 *Fate in air*

Proquinazid is slightly to moderately volatile according to its vapour pressure and Henry's law constant. Volatilisation from dry soils appears insignificant and a volatilization of up to 14% from plant surfaces was observed. Proquinazid is not expected to be subject to long range transport due to its rapid degradation (4 hours) by photochemical oxidation in air.

3.3.2 ENVIRONMENTAL EXPOSURE

3.3.2.1 *Soil*

PEC values have been calculated for an application rate of 2 x 50g a.s./ha with 50% interception (plant cover) and a 14 day interval between applications (less than the recommended 4 weeks in the Norwegian GAP). Worst case laboratory degradation rates and formation fractions of metabolites were used. The Finnish PECsoil calculator was used to stipulate the maximum PECsoil of proquinazid and its metabolites, using an application interval of 28 days and a continuous annual use over 20 years. The predicted initial environmental concentrations (PIEC) calculated were similar to the values calculated by the applicant. The following values, in mg/kg, were obtained:

Proquinazid:	PECsoil, max = 0.370,	initial = 0.066
IN-MM671:	PECsoil, max = 0.111,	initial = 0.027
IN-MM986:	PECsoil, max = 0.0056,	initial = 0.004
IN-MM991:	PECsoil, max = 0.0045,	initial = 0.002

The Finnish PECsoil calculator estimated increasing concentrations of proquinazid and IN-MM671 in soil until approximately 10 years of use, after which a plateau ("steady state") concentration was reached at 0.25–0.30 mg/kg (proquinazid) and 0.08 mg/kg (IN-MM671).

3.3.2.2 *Groundwater*

The leaching behaviour of proquinazid and its metabolites was assessed with FOCUS PELMO in winter and spring cereals. The models were run with an application rate of 2 x 50 g a.s./ha, plant cover of 50/70% and an application interval of 14 days. The 80 percentile concentration of the substances at 1 meter was <0.001 µg/L in all scenarios.

3.3.2.3 *Surface water*

Models developed by EU's working group FOCUS estimate predicted environmental concentrations in surface water and sediment in different scenarios. PEC values have been calculated for the use in spring and winter cereals at an application rate of 2 x 50g a.s./ha with 50/70% interception and a 14 day interval between applications (less than the recommended 4 weeks in the Norwegian GAP).

The main route of exposure for proquinazid was spray drift. The maximum PECsw values for proquinazid at Step 1, 2, 3 and 4 were 2.76, 0.46, 0.32 and 0.17 µg/L. Corresponding PECsed values were 241, 26.1, 3.65 and 3.65 µg/kg. The metabolite IN-MM671 had PECsw values of 3.09, 0.33 and 0.16 µg/L at Step 1, 2 and 3. Corresponding PECsed were 90.0, 9.89 and 1.00 µg/kg. For the metabolites IN-MM986, IN-MM991 and IN-MT884, PECsw values at Step 2 were 0.15, 0.14 and 0.20 µg/L, respectively. The corresponding PECsed values were 3.51, 0.38 and 1.36 µg/kg.

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 active substance (or studies are only conducted with the product), or identified metabolites are more toxic than the active substance, these calculations are

included in the summary below. If this is not the case, these values and calculations are omitted.

For mammals and birds, the risk assessment is performed according to the EU Guidance Document for Birds and Mammals (EFSA 2009). The EU triggers (birds and mammals) are $\geq$10 and $\geq$5 for TER_{acute} and $TER_{chronic}$, respectively.

3.3.3.1 *Mammals*

Proquinazid has low acute toxicity to mammals (LD50: 4846 mg/kg bw/d) and the 2-generation reproductive NOEC is 35.1 mg/kg bw/d. Proquinazid pass the EU trigger value for acute exposure (TER_{acute} >409) and chronic exposure ($TER_{chronic}$ =9.0) calculated according to the EU Tier 1 scenarios.

3.3.3.2 *Birds*

Proquinazid has low acute toxicity (LD50: >2250 mg a.s./kg bw) and is toxic in a short-term dietary toxicity study (LC50: 1371 mg/kg bw/d). In a chronic toxicity test, the NOEC was 7.78 mg a.s./kg bw/d. Proquinazid pass the EU trigger values for acute and chronic exposure (TER_{acute} >600, $TER_{chronic}$ =5.16) according to the EU screening step with an application rate of 2x50 g a.s./ha in cereals.

3.3.3.3 *Bees*

Proquinazid shows low contact (LD50: >197 µg/bee) and oral toxicity to bees (LD50: >125 µg/bee). Hazard quotients for contact (Qhc) and oral exposure (Qho) are estimated to be 0.25 and 0.4 respectively. These pass the trigger value (<50).

3.3.3.4 *Non-target arthropods*

In Tier 1 laboratory acute contact toxicity studies the trigger of >30% effect is exceeded for foliage predatory mites. Extended lab studies did not show effects above the trigger effect level of 50 %. Hazard Quotients based on the LR50 values from the laboratory studies passed the HQ trigger (2) for in-field and off-field.

3.3.3.5 *Earthworms*

Proquinazid is acutely toxic to earthworms ($LC50_{corr}$: >500 mg/kg d.w. soil).). TER_{acute} is estimated to be 1351, which pass the trigger (≥10). The NOEC from a chronic toxicity study with Talius (200 g/L proquinazid) was 25.45 mg a.s/kg d.w. soil. TER is estimated to be 69. This value passes the trigger (≥5).

3.3.3.6 *Other soil macro organisms*

Further studies on soil macroorganisms are required if DT90 from field studies is between 100 and 365 days and HQ arthropods is >2. As this is not the case for proquinazid no studies on other soil macroorganisms are required.

3.3.3.7 *Microorganisms*

The effects of Talius on microbial mediated carbon and nitrogen mineralization in soil were investigated in laboratory tests. No significant effects above the 25% trigger after 28 days were seen. No significant effects were seen on the degradability of soil organic matter in a 12 month field litter bag study under exposure conditions simulating 10 years continual use of Talius at an annual rate of 67.5 and 75 g a.s./ha.

3.3.3.8 *Terrestrial plants*

Results from glasshouse studies using Talius at a rate of 75 - 100 g a.s/ha showed that there were no significant herbicidal effects on a range of terrestrial plants tested (<50% phytotoxicity).

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 active substance (or studies are only conducted with the product), or identified metabolites are more toxic than the active substance, 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 (without extra buffer zones) and the lowest acute (LC50 or EC50) or chronic (NOEC) values for the different organism groups. A tiered approach is applied, where TER based on Step 1 first is calculated. If the TER fails the triggers, Step 2 is calculated and so on. The EU triggers for TER_{acute} and $TER_{chronic}$ are $\geq$100 and $\geq$10, respectively.

3.3.4.1 *Fish*

Proquinazid has very high acute (LC50: 0.349 mg a.s./L) and high chronic (NOEC: 0.0030 mg a.s./L) toxicity to fish. Acute TER calculations for proquinazid pass the EU triggers based on Step 1 surface water scenarios. $TER_{chronic}$ for proquinazid pass the EU triggers based on Step 4 surface water scenarios with a 3 meter buffer zone.

3.3.4.2 *Invertebrates*

Proquinazid has very high acute (EC50 0.11 mg/L) and chronic (NOEC 0.0018 mg a.s./L) toxicity to aquatic invertebrates. Acute TER calculations pass the EU trigger based on Step 2 FOCUS surface water scenarios. For the chronic risk assessment proquinazid pass the trigger based on FOCUS Step 4 scenarios with a buffer zone of 3 meter.

3.3.4.3 *Sediment dwelling organisms*

Chronically toxic to *Chironomus riparius* larvae (28 d NOEC: 0.456 mg a.s./L (spiked water)). TER calculations for proquinazid pass the EU trigger based on Step 1 FOCUS surface water scenarios.

3.3.4.4 *Aquatic plants*

No significant inhibitory effects on the growth and reproduction of *Lemna gibba* were observed when exposed to 0.2 mg a.s./L for 14 days. TER calculations for proquinazid pass the EU trigger based on Step 1 FOCUS surface water scenarios.

3.3.4.5 *Algae*

Proquinazid shows very high toxicity to green algae (120h EC50: 0.25 mg a.s./L). TER calculations for proquinazid pass the EU trigger ($\geq$10) based on Step 1 FOCUS surface water scenarios.

3.3.4.6 *Microcosm/Mesocosm studies*

No microcosm or mesocosm studies have been submitted.

3.3.4.7 *Bioconcentration*

Proquinazid shows a high potential for bioconcentration (BCF: 821) and has depuration time (CT_{95}) of 5.8 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 it was stated that VKM in particular should look at the following:

The human health risk for operators related to the properties of the active substance and the product. VKM is in particular asked to look at the following:

- The effects seen in studies on dog and if these effects warrant a classification for chronic toxicity.
- The oncogenic effects in liver and thyroid.
- The establishment of NOAELs and reference values (ADI, AOEL and ARfD).
- Dermal absorption.
- The classification and labeling of the active substance and the product.

VKM discussed the above mentioned points.

4.1.1 THE EFFECTS SEEN IN STUDIES ON DOG

VKM discussed the seriousness of the effects in studies with dogs and concluded that less serious effect (dose-related ocular discharge increase) was seen in dogs in both the 90 days study and 1 year-study. The effect was also discussed in ECHAs CLH report for proquinazid with the similar conclusion.

4.1.2 THE ONCOGENIC EFFECTS IN LIVER AND THYROID

Exposure to proquinazid was found to induce thyroid tumors in male rats, and hepatocellular adenomas and liver cholengiocarcinomas in female rats. The tumors are occurring in the two highest dose groups.

In mice, a slight increase in liver tumors was observed at the highest dose.

VKM supports the view that the rat thyroid tumors are not relevant for humans. This is based on the consideration that rats are exceptionally sensitive to the induction of this tumor type, and the observed increase in TSH and decreases in T3 and/or T4 in exposed rats.

Hepatocellular adenomas are known to have the capability to transform into carcinomas. VKM has no data or information suggesting that the hepatocellular tumors, as well as the liver cholengiocarcinomas are irrelevant to humans, and supports the suggested classification by ECHA.

4.1.3 ESTABLISHMENT OF REFERENCE VALUES

NOAEL

VKM propose an NOAEL of 1.2 mg/kg bw/day for proquinazid based on the 2 year study with rat and is of the opinion that the test substance-related increase in non-neoplastic liver lesions is relevant for humans.

ADI

An ADI of 0.01 mg/kg bw/day is proposed for proquinazid based on applying a 100-fold uncertainty factor to NOAEL of 1.2 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). VKM support the proposed ADI value.

AOEL

An AOEL of 0.02 mg/kg bw/day is proposed for proquinazid based on applying a 100-fold uncertainty factor to the NOAEL of 2 mg /kg bw/day determined in the 90-day feeding study in rats. VKM support the proposed AOEL value.

AR_fD

An AR_fD of 0.2 mg/kg bw/day is proposed for proquinazid based on ocular discharge in one dog at 19 mg/kg bw/day in the first week of the 90-day study and a 100 fold uncertainty factor. VKM supports the proposed AR_fD value.

4.1.4 DERMAL ABSORPTION

VKM supports The Norwegian Food Safety Authority proposal of dermal absorption in vivo in rats to include residues in all tape strips except the two outermost, using data from the end of the study. For the in vitro calculations, all tape strips are included as residues in the individual tape strips were not reported. Dermal absorptions of 3.25 % for the formulated product and of 29.45 % for the diluted product tested are used in the calculation of the operator exposure. Norwegian directions for use give a 2.6 times higher dilution than the dilution tested.

4.1.5 THE CLASSIFICATION AND LABELLING OF THE ACTIVE SUBSTANCE AND THE PRODUCT.

Proquinazid has recently (2012) been classified with (Xn;R40) in ECHA.

The proposed classification from The Norwegian Food Safety Authority is: **Xn;** Carc. Cat. 3, R40 (Possible risks of irreversible effects)

VKM support the proposed classification from The Norwegian Food Safety Authority.

4.2 HEALTH RISK CHARACTERIZATION

4.2.1 HEALTH RISK DUE TO HUMAN EXPOSURE

VKM has based their risk characterization for operators on the summary from Norwegian Food Safety Authority presented in section 5.3 and on the exposure- and dose-response assessments presented in section 5.2.1 by applying the scale of exceed of AOEL.

4.2.2 OPERATOR, WORKER AND BYSTANDER EXPOSURE

4.2.2.1 *Operator exposure*

AOEL is exceeded in both models without PPE and is still exceeded when using gloves in the UKPOEM. However the results from the German model shows that AOEL is not exceeded

when using PPE (gloves+coveralls and sturdy footwear). The operator exposure, when using mechanical spraying in cereal, was estimated based on the UK POEM and the German model.

AOEL is exceeded in both models without PPE, with 65 % with the results from UK Poem and with 30% with the results from the German model. The use of PPE (gloves+coveralls and sturdy footwear) reduces the exposure to under the AOEL with the results from the German model and to 5% with the results with PPE (gloves) from UK Poem.

4.2.2.2 *Re-entry and bystander exposure*

Bystander exposure calculations for grapes (worst case) gave a value of <<1% of the AOEL. Manual activities before harvest in cereals are rare. Worker exposure calculation in grapes with re-entry activities gave a value of < 1% of the AOEL.

4.2.3 HEALTH RISK DUE TO RESIDUES IN PRODUCTS FOR CONSUMPTION

Not included in the terms of reference.

4.3 ENVIRONMENTAL FATE ASSESSMENT

4.3.1 DEGRADATION IN SOIL

In aerobic laboratory studies, proquinazid was shown to have a medium to high persistence in soil with normalised half-lives between 24 and 239 days (geometric mean of 60 days). The degradation of the metabolite IN-MM671, is moderate with DT50 (geomean) 81 days. For IN-MM986 and IN-MM991 the degradation is medium with DT50 (geomean) 16 days) and 22 days respectively. Four field studies were performed across Northern and Southern Europe. The observed half lives in field studies are lower than those found in laboratory studies. DT50 values for proquinazid ranged from 5.5-70 days (geometric mean 22 days) and DT90 ranged from 18-231 days. Photolysis may be an important route of degradation for proquinazid in soil. The dissipation rates of the metabolites IN-MM671, IN-MM986 and IN-MM991 were as follows: moderate (geomean 153 days), medium (geomean 40 days) and moderate (geomean 75 days). Two soil accumulation studies were conducted in northern and southern Europe. No residues of proquinazid or any of the metabolites were detected, with the exception of IN-MM671,which was found in the soil sample of one site at a concentration of 0.006 mg/kg. EFSA has concluded that proquinazid is not expected to accumulate in soil. However calculations made with the Finnish PEC calculator indicate a potential for accumulation of proquinazid and IN-MM671 up to an equilibrium level after approximately 10 years of annual applications under the conditions simulated in the model. The VKM considers the results from the Finnish PECsoil calculator to be relevant and expects that accumulation may occur under Norwegian conditions.

4.3.2 MOBILITY IN SOIL AND LEACHING TO GROUNDWATER

Sorption studies indicate low mobility in soil for both proquinazid and its metabolites. This is supported by model calculations showing groundwater concentration <0.001 µg/L. Hence, the potential for groundwater contamination is assumed to be low.

4.3.3 SURFACE WATER CONCENTRATIONS

Step 4 calculations were performed only for proquinazid where a 90th percentile worst case drift event and a 3 m buffer zone were used. The main route of exposure for proquinazid was spray drift. The maximum PEC_{sw} values for proquinazid at Step 1, 2, 3 and 4 were 2.76, 0.46, 0.32 and 0.17 µg/L. Corresponding PEC_{sed} values were 241, 26.1, 3.65 and 3.65 µg/kg. The Panel considers these maximum PEC values to be relevant for aquatic risk assessment.

4.4 ENVIRONMENTAL RISK CHARACTERIZATION

The risk characterization of the product's ecotoxicological effects on terrestrial and aquatic organisms made by VKM is based on the summary from the Norwegian Food Safety Authority presented in section 5.3 and exposure-, dose/response assessments and risk scale described in section 5.2.2.

4.4.1 EFFECTS AND RISKS TO TERRESTRIAL ORGANISMS

VKM concludes that there is minimal risks for toxic effects of proquinazid to mammals, birds, bees, earthworms, plants and soil microorganisms with the proposed application regime.

In standard laboratory studies with non-target arthropods proquinazid showed effects above the trigger of >30% for predatory mites. Extended laboratory studies on parasitoids and leaf dwelling predators did not show effects above the trigger effect level of 50 % at relevant application rates. Hazard Quotients (HQ) based on the LR50 values passed the HQ trigger (2) for in-field and off-field. VKM concludes that there are minimal risks for toxic effects of Talius to terrestrial organisms with the proposed application regime.

4.4.2 EFFECTS AND RISK TO AQUATIC ORGANISMS

VKM concludes that there is minimal risk for toxic effects of proquinazid to sediment dwelling organisms, aquatic plants, and algae with the proposed application regime. For fish and invertebrates minimal risks are calculated provided that a 3 m buffer zone is used.

VKM also notes that proquinazid shows a high potential of bioconcentration in fish (BCF= 821). However, the depuration is rapid (CT_{95} = 5.8 days). Furthermore, proquinazid dissipates rapidly from the water phase and the panel concludes that the proposed application regime is not likely to cause significant bioaccumulation of proquinazid in fish.

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 a less serious effect (dose-related ocular discharge increase) was seen in dogs in both the 90 days study and 1 year-study.

The opinion of the Panel is that Cholangiocarcinomas is relevant for the classification of cancer and VKM is concerned about these effects.

VKM proposes an NOAEL of 1.2 mg/kg bw/day for proquinazid based on the 2 year study with rats.

VKM support:

- The proposed ADI value of 0.01 mg/kg bw/day.
- The proposed AOEL value of 0.02 mg/kg bw/day.
- The proposed AR_fD value of 0.2 mg/kg bw/day.
- The proposed classification from The Norwegian Food Safety Authority.

VKM supports The Norwegian Food and Safety Authority calculations for dermal absorption under Norwegian directions for use (2.6 times higher dilution).

5.2 ENVIRONMENT

Proquinazid can be persistent under prevailing conditions in Norway and the Panel considers the results from the Finnish PEC calculator to be relevant for Norwegian conditions and expects that repeated annual applications may cause accumulation in soil up to an equilibrium level under Norwegian conditions.The potential for groundwater contamination from leaching of proquinazid and its metabolites is low.

There are minimal risks for toxic effects of proquinazid to terrestrial organisms, sediment dwelling organisms, aquatic plants, and algae with the proposed application regime.

For fish and invertebrates minimal risks are calculated provided that a 3 m buffer zone is used.

Attachment

Attached is The Norwegian Food Safety Authority's evaluation of the documentation submitted by the applicant, folowing application for registration of the fungicide Talius. (www.Mattilsynet.no)