Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

Risk assessment of the pesticide Envidor with the active substance spirodiclofen

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

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SUMMARY

Envidor is a new product in Norway containing the active substance spirodiclofen. The product is applied for use as an insecticide and acaricide in fruit, berries and ornamentals (field, glasshouses and tunnels). The Norwegian Scientific Committee for Food Safety (VKM) was asked by the Norwegian Food Safety Authority to perform a risk assessment on human health, environmental fate and ecotoxicological effects of the active substance and the product. The risk assessment of the product was finalized at a meeting November 25, 2010, by VKM's Scientific Panel on plant protection products (Panel 2). VKM Panel 2's conclusion is as follows:

Both Envidor and the active substance spirodiclofen showed low acute oral -, dermal - and inhalation toxicities in animal studies, but showed skin sensitising properties. The estimated risk for operators is assessed as minimal provided adequate use of personal protective equipment.

Spirodiclofen may have endocrine disrupting effects, but the *in vivo* data are not sufficient to make a firm conclusion at this point. Adrenals and other organs of the endocrine system, including the reproductive system, are target organs for chronic toxicity of spriodiclofen. Males seem to be more sensitive than females for adverse reproductive effects of spirodiclofen. Decreased testes and epididymides sizes, testes atrophy and decreased number of sperm were seen both in the parental and subsequent generation of rats. No teratogenic effect of spirodiclofen was seen.

The disturbances in the endocrine system may account for the carcinogenic potential of spirodiclofen as evidenced by tumours in testicles, uterus and liver of animals. Spirodiclofen is not considered genotoxic. The Panel regards spirodiclofen to be carcinogenic and toxic to the reproduction in laboratory animals.

Both spirodiclofen and its metabolites are rapidly degraded in soil, but while spirodiclofen has a low mobility due to high soil sorption, its metabolites are highly mobile.

Use of Envidor with the proposed application regime implies a very high risk for adverse effects on bees and non-target arthropods due to exposure to the active substance spirodiclofen. The risk for adverse effects of spirodiclofen on other terrestrial organisms, and on aquatic organisms provided that a buffer zone of 30 m to surface water is applied, is considered to be minimal.

CONTRIBUTORS

Persons working for VKM, either as appointed members of the Committee or as ad hoc experts, do this by virtue of their scientific expertise, not as representatives for their employers. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

Assessed by VKMs Panel on plant protection products (Panel 2)

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1. 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 11, 2010 for VKM to perform a risk assessment on use of the pesticide Envidor 240 SC containing the active substance spirodiclofen. Both the environmental and the health risk assessments of the product were finalized by VKM's Panel 2 at a meeting on November 25, 2010.

2. TERMS OF REFERENCE

Terms of reference as provided by the Norwegian Food Safety Authority are as follows: "Envidor 240 SC is a new product in Norway containing the new active substance spirodiclofen. The product is applied for use as an insecticide and acaricide in fruit, berries and ornamentals (field, glasshouses and tunnels). In this regard, the Norwegian Food Safety Authority asks for an assessment of the following:

- *The human health risk for operators related to the properties of the active substance and the product. The Norwegian Food Safety Authority would also like a statement on the inherent properties of the product, and a statement on the effects related to the limitations in the modelling. The Panel is in particular asked to look at the reproductive and carcinogenic effects of spirodiclofen.*
- *The fate and behaviour in the environment and environmental risk with regard to the properties of the active substance spirodiclofen and the product Envidor 240 SC. The Panel is in particular asked to look at the toxicity and risk to non-target arthropods and bees."*

3. RISK ASSESSMENT

3.1. Background documentation

The Panel's risk assessment is based on the Norwegian Food Safety Authority's evaluation (2010) of the documentation submitted by the applicant. The Norwegian Authority for Food Safety publishes both their evaluation of Envidor and their final regulatory action on the registration of the pesticide product at their homepage http://www.mattilsynet.no.

3.2. 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 summary report on hazard identification, hazard characterization and assessment of exposure, which is included in the present document, is then reviewed by VKMs Panel 2. This review may result in some amendments in the original documents of both the summary report and the full report

issued by the Norwegian Food Safety Authority (2010). The fourth step (risk characterization) is based on the three first steps and is the Panel's conclusions or risk assessment.

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 Europoem, 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). The Panel uses the 75 percentile of exposure assessment for both UK poem and German model. The Panel has to base their assessment on the models whenever exposure data for the product is not presented.

The Panel 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 risk of operator exposure, the Panel makes use of a risk 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 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 Panel 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.

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 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 compartment 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 EUs FOCUS-scenarios. The models produce maximum PNEC and average PNEC calculated for specified periods after pesticide application. In the surface water scenarios PNEC 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 **exceeds** 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.

The Panel 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, the Panel 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.

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

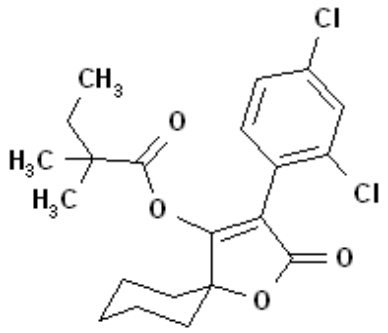
Envidor 240 SC is a new product in Norway containing the new active substance spirodiclofen. The product is applied for use as an insecticide and acaricide in fruit, berries and ornamentals (field, glasshouses and tunnels). The Norwegian Institute for Agricultural and Environmental Research recommend the applied uses.

The standardized area dose is 60 ml (14.4 g a.s.) per decare. There should be maximum one application at uses on field, and maximum two applications at uses in glasshouses and tunnels. The application equipment differs on the crop, and can be tractor-mounted sprayers as well as handheld sprayers.

Spirodiclofen belongs to the IRAC chemical group 23: Tetronacid- and tetra-acid-derivates. The mode of action differs from other commercial insecticides on the Norwegian marked, but there will still be a potential risk of resistance.

3.3.1. Identity and physical/chemical data

Product name	Envidor 240 SC
Active substance	Spirodiclofen
Formulation	Suspension concentrate

Concentration of active substance	240 g/L
CAS number	148477-71-8
IUPAC-name	3-(2,4-dichlorophenyl)-2-oxo-1-oxaspiro[4.5]dec-3-en-4-yl 2,2-dimethylbutyrate (ISO) 3-(2,4-dichlorophenyl)-2-oxo-1-oxaspiro[4.5]dec-3-en-4-yl 2,2-dimethylbutanoate (ACD)
Structural formula	
Molecular mass	411.3 g/mole
Solubility in water	Low 0.00019 mg/L (20°C, pH 7)
Vapour pressure	Low $3x10^{-7}$ Pa (20°C)
Henrys constant	Medium < 2 x 10^{-3} Pa m^3/mol
log Pow	High 5.1 (20°C, pH 7)
pKa	Could not be determined, no dissociation is expected

3.3.2. Mammalian toxicology

Spirodiclofen

Toxicokinetics

Absorption: The excretion of radioactivity in urine indicates that after a single oral dose of 2 mg/kg bw at least 64% (males) or 76% (females) of spirodiclofen is absorbed within 48 h. In another study at least 60% (males) or 75% (females) of the administered spirodiclofen was absorbed within 24 h. If the amount in bile is included the absorption in males is increased to 70%. The faecal excretion of radioactivity in bile-duct cannulated rats treated with a single oral dose of 1 mg/kg bw of spirodiclofen suggests incomplete absorption. The level of absorption seems to decrease with increasing oral doses and after pretreatment with a high dose.

Distribution: Levels of radioactivity in organs and tissues were low, and the relative distribution was similar for all experimental groups. Depending on the time of sampling peak tissue levels

were observed at 3-8 h after administration. Highest levels of radioactivity were observed in liver, kidney, plasma, gastrointestinal tract and skin. In females, organ and tissue levels were 5-15 times lower than in males. In male rats treated with spirodiclofen for 15 days, tissue levels were about 4 times lower than in males treated with a single dose of spirodiclofen. Only traces of radioactivity was found in the testis (0.003 pg/g) and nothing were detected in other organs involved in hormonal regulation (e.g. in the adrenal and thyroid gland).

Metabolism: A marked sex difference in metabolite profile was observed. The main metabolite in female rats was M01 (54.8%), while this metabolite only represented 2.3 - 3.8% in males. In male rats the major metabolites were the M02 and M03 isomers, representing 55.1 - 57.4% of total radioactivity. In females these metabolites only represented 17.3%, indicating a higher capacity in further metabolization of the enol metabolite in male rats. In plasma, liver and kidney samples of males as well as females enol was the main metabolite. The parent compound was not detected in urine or bile. In faeces it accounted for 3.4 % in male and 0.4% in female rats pre-treated with 50 ppm and 5.7% in male and 16% in female rats pre-treated with 2500 ppm.

Excretion: Following administration of 2 mg ^{14}C-spirodiclofen/kg bw to male rats at least 88% of the administered dose (99% of recovered radioactivity) was excreted within 48 h. After administration of 100 mg spirodiclofen /kg bw, 96% of the administered dose (100% of recovered radioactivity) was excreted within 168h. Elimination half-life was 3.5-5.3 hours.

Acute toxicity

Spirodiclofen has low acute toxicity to rats following oral, dermal or inhalative administration.

Irritation and sensitisation

Spirodiclofen is considered not irritating to skin and eye, but it exhibits a skin sensitising potential and meets the criteria for classification as **Xi; R43 May cause sensitisation by skin contact**.

Genotoxicity

Spirodiclofen did not induce mutations in bacteria. The point mutations test in mammalian cells in vitro gave equivocal results. Statistically significant increases in mutant frequency were observed in one culture with and one culture without metabolic activation. The results were not reproduced in parallel treated cultures or in a second trial, and it was no dose-response. To exclude the possibility of point mutations in vivo however, a second in vivo test would have been preferable. The results of the chromosomal aberration study in mammalian cells in vitro were also equivocal. A statistically significant increase in aberrations were observed (+/-S9), but the values are within the range of historical controls. Spirodiclofen was found to be negative in an in vivo micronucleus test. Based on these results, spirodiclofen is considered to be non-genotoxic.

Sub-chronic and chronic toxicity

The adrenals, where effects on weight and/or histopathology are observed already at low doses, seem to be target organs in both rats, mice and dogs. Effects on the adrenals were observed both in sub-chronic and chronic studies. In addition to the adrenals also other organs of the endocrine system, included reproductive organs, were affected in all test species. Effects on haematological and clinical biochemical parameters included reduction of cholesterol and triglyceride levels were also observed.

Carcinogenicity

Spirodiclofen is considered carcinogenic for inducing Leydig cell tumours and uterus adenocarcinomas in the rat (NOAEL 14.72 mg/kg bw/day), and for inducing liver tumours in the

mouse (NOAEL 4.1 mg/kg bw/day). Classification as **Xn; R40 Limited evidence of carcinogenic effect** is proposed.

Reproductive toxicity and teratology
Critical effects in F0 animals in the 2-generation study in rats were decreased body and liver weight and decreased blood cholesterol in males and decreased triglyceride concentration in both males and females. In F1 males effects on the testes and epididymides were observed at all dose levels. In the highest dose group, effects on spermatogenesis in F1 males were observed, and four males failed to reproduce. Based on the reproductive effects, spirodiclofen fulfil the criteria for classification as **Xn; R60 May impair fertility / R62 Possible risk of impaired fertility**.

In the teratology study in rats no adverse effects were observed at any dose level. Critical maternal effect in the rabbit study was a significant decrease in body weight in the two highest dose groups. The critical developmental effect was an increased incidence of liver lobulation in foetuses of the highest dose group, with a NOAEL (developmental) of 300 mg/kg bw/day. Spirodiclofen is not considered as teratogenic.

Neurotoxicity
Spirodiclofen is not considered neurotoxic. No effects were observed in the acute or developmental neurotoxicity studies. In the sub-chronic study decreased foot splay and grip strength and reduced motor and locomotor activity were observed, but only at high doses and in the presence of general toxicity. The functional observational battery test conducted in the combined study on chronic toxicity and carcinogenicity in Wistar rats did not reveal any relevant signs or symptoms indicating evidence for neurotoxic potential of spirodiclofen.

Special studies
Based on the mechanistic studies, the notifier concluded that M01 interferes with steroid hormone synthesis at the level of general biochemical pathways /pyruvate/citrate shuttle (Krebs cycle) but has no direct effects on steroid synthesis. In addition, the notifier concluded that decreased levels of reducing equivalents (e.g. NADH and NADPH) unspecifically lower the synthesis of cholesterol, triglycerides and steroid hormones. Inhibition of steroid hormone biosynthesis increases the release of adrenocorticotrophins and gonadotrophins from the pituitary gland. The increase in gonadotrophins then results in chronic stimulation of testicular Leydig cells and uterine cells, resulting in hypertrophy, hyperplasia and tumour formation. These considerations seem plausible, and it can be concluded that the carcinogenic potential of spirodiclofen should be regarded as a non-genotoxic carcinogenic mechanism. Because of the interference with steroid hormone synthesis, spirodiclofen should be regarded as an endocrine disruptor.

Medical data
No reports about human findings are available and a specific antidote is not known. In case of oral uptake, first aid measures should consist of removal of ingested compound by gastric lavage or induction of vomiting and symptomatic treatment. Contaminated skin should be washed immediately with plenty of water.

Envidor 240 SC

Co-formulants
Spirodiclofen does not contain co-formulants occurring above the limit that trigger labelling according to the dangerous substance list.

Acute toxicity
Envidor 240 SC has low acute toxicity to rats following oral, dermal or inhalative administration.

Irritation and sensitisation
Spirodiclofen is considered not irritating to skin and eye, but it exhibits a skin sensitisation potential (classified as **Xi; R43 May cause sensitisation by skin contact**).

Dermal absorption
Based on the in vitro study with human skin the dermal absorption is 0.6% for the concentrate and 7% for the dilution. The monkey studies were regarded as being of limited value because of dose selection, low recovery in the main study and limited number of experimental animals.

Operator, worker and bystander exposure

UK Poem estimate of exposure suggests that the level of exposure will be acceptable for operators without PPE for application using tractor-mounted sprayers. Because of the sensitising properties of Envidor 240 SC (**Xi; R43**) however, gloves should always be used when handling the product. For application with handheld sprayers the UK POEM estimate of exposure requires gloves to be worn during mixing and loading and during application in fruits and berries. In ornamental plants, AOEL is exceeded even when full protective equipment (gloves and impermeable coverall) is used.

Worker exposure following re-entry estimated using an exposure model proposed by Hoernicke et al. (1998) and Krebs et al. (2000) show that the exposure is acceptable without use of PPE. Although the estimated worker exposure is below the AOEL however, use of gloves should be worn to minimize exposure and because of the sensitising properties of Envidor 240 SC. Estimation of bystander exposure using EUROPOEM II shows that bystanders are not at risk.

3.3.3. Residues in food and feed

This is not included in this report.

3.3.4. Environmental fate and ecotoxicological effects

Environmental fate and behaviour

Degradation in soil
The degradation rate of spirodiclofen is high to moderate, DT50: 1-13 days, geometric mean DT50: 5.4 days. DT90: 3.8-44 days, geometric mean 18.4 days. The per cent mineralization of spirodiclofen is high 23-93 % of AR and the formation of bound residues is between 7 and 14 % of AR. Four main metabolites were observed and the following DT50-values were calculated. BAJ 277740-enol: 1.9-9.8 days. BAJ 2740-ketohydroxy: 0.6-27 days. BAJ 2740-dihydroxy: 3.8-30 days. 2,4-dichlorobenzoic acid: 3.5-11 days. An anaerobic soil degradation study has not been performed. DT50lab (10°C, aerobic) was calculated from DT50lab (20°C, using a Q10 factor of 2.58). The degradation rate is high to moderate, DT50: 2.8- 34 days. DT90: 10-114 days. Photolysis is not an important route of degradation for spirodiclofen. No field studies were submitted on the basis that the laboratory degradation of spirodiclofen and major metabolites is <60 days.

Sorption/mobility
The sorption of spirodiclofen to soil can be classified as very high with a Koc-value of 31037. The sorption of the metabolites BAJ 2740-enol, BAJ 2740-dihydroxy and 2,4-dichlorobenzoic acid can be classified as low, while the sorption of BAJ 2740-ketohydroxy can be classified as moderate. An aged column study is performed. Based on the amount of radioactivity in the leachate, the mobility of spirodiclofen is low and the mobility of the main metabolites is high.

Degradation in water
The hydrolysis of spirodiclofen is moderate at pH 7. In sterile aqueous buffer solutions, spirodiclofen hydrolysed with first order DT50 of 120 (pH 4), 52 days (pH 7) and 2.5 days (pH 9) at 20 °C. The hydrolytic stability of spirodiclofen decreases as temperature and pH increase. Photolysis is not an important degradation pathway for spirodiclofen. No study is submitted on ready biodegradability. The low formation rate of CO_2 in aerobic water-sediment studies (2.1-2.6 %) suggests that the substance is not readily biodegradable.

The degradation of spirodiclofen for the whole water sediment system can be classified as high with DT50: 2.3-4.2 days. DT90: 7.5-14 days. Mineralization was at low level and only small amounts of bound residues was formed. Spirodiclofen quickly partitioned into sediment. The major metabolite was BAJ2740-enol, with maximum levels of 84% of AR and 30% of AR in water and sediment, respectively. DT50 values for BAJ 2740-enol in the pond system were 393 days and in the pit system, no degradation of BAJ 2740-enol was apparent until study end.

Fate in air
Measured volatilisation of spirodiclofen from soil and leaf surfaces under field conditions was negligible DT50air: 2.7 hours. Vaporization: Henry's Law constant: 2×10^{-3} Pa/mol m^3. The data suggested that the concentrations of spirodiclofen are likely to be negligible.

Exposure

According to a simple model recommended by the EU working group FOCUS the expected PIEC, predicted initial environmental concentration, in soil is 0.096 mg a.s./kg after the application of 144 g a.s./ha with 50 % interception.

Groundwater
The leaching behaviour of Spirodiclofen was evaluated using all the nine FOCUS groundwater scenarios and the two recommended models, i.e. FOCUS-PELMO (version 3.3.2) and FOCUSPEARL (version 2.2.2). The use considered was Envidor in apple according to the representative GAP, i.e. a single application of 144 g a.s./ha. The interception was 65%, thus the application rate used for all scenarios was 144 g a.s./ha x 35%, or 50 g a.s./ha. These modelling assessments indicate that a contamination of groundwater of spirodiclofen and its metabolites is unlikely to occur.

Surface water
PECsw of spirodiclofen was recalculated by the RMS using the following assumptions.

(i) Single application of 144 g a.s./ha (orchard crops).

(ii) Entry into surface water via drift, based on 90th percentile drift values taken from the Guidance Document on Aquatic Ecotoxicology (8075/VI/97 rev 8); drift values for early and late stage for orchard crops..

(iii Equal distribution in a static water body of 30 cm depth.

(iv) $DT50_{dissipation}$ of 1.1 days from water (maximum 1st order DT50 from water phase).

Under the above assumptions, early application of Envidor according to GAP will lead to PEC_{SW} values for Spirodiclofen for instance of 14 µg/L for 3 m buffer zones. The initial PEC_{SW} of the metabolite BAJ 2740-enol was derived from that of the active substance, with corrections for the difference in molecular mass (correction factor 313.2/411.3) and the maximum percentage at which the metabolite was formed from the parent substance in the water phase of water/sediment systems (84% of AR).

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.

Mammals

Low acute toxicity to mammals (LD50: >2500 mg/kg bw/d). TER for the indicator species small herbivorous mammal in orchards is estimated as >147. This value does not exceed the trigger (<10). Chronically toxic (NOEC: 29.6 mg/kg bw/d). TER is estimated to be 6.1. This TER does not exceed the EU trigger (<5).

Birds

Low acute toxicity to birds (LD50: >2000 mg/kg bw/d). TER for the indicator species small insectivorous bird in orchards is estimated as >257. This value does not exceed the EU trigger (<10). Moderate dietary toxicity (LC50: >1061 mg/kg bw/d). TER for the indicator species in orchards is estimated as >244. This value does not exceed the trigger. Chronic toxicity (NOEC: 51 mg/kg bw/d). A reproductive toxicity study showed no effects on reproductive parameters up to and including the highest does level. TER is estimated to be 12. This value does not exceed the EU trigger (<5).

Bees

Low contact (LD50: >200 µg/bee) and oral toxicity to bees (LD50: >196 µg/bee). Hazard quotients for contact (Qhc) and oral exposure (Qho) are estimated to be <0.72 and <0.73 respectively. These do not exceed the trigger value of more than 50. However, semi-field and field studies show that populations of honey bees are adversely affected (i.e., brood development, pupal abundance). An effect on bee brood, even if temporary, can have a long-lasting effect on the colony.

Non-target arthropods

In Tier 1 laboratory acute contact toxicity studies, Envidor showed 100% effects on predatory mites. Extended lab studies showed effects above the trigger effect level of 50%. The Hazard Quotient based on the lowest LR50 for *Typhlodromos pyri* was estimated to be 60 (in-field) and exceeds the HQ trigger (2). HQs for off-field exceed the HQ trigger (2) up to a distance of 30 and 20 meters from the field for fruit crops late and fruit crops early, respectively. Two field studies showed significant reduction in abundance of *Typhlodromos pyri* after 27 and 89 days, respectively. Recovery was observed within one year.

Earthworms
Low acute toxicity to earthworms (LC50: >1000 mg/kg d.w. soil). TER is estimated to be 10417. This value does not exceed the trigger (<10).

For other soil organisms, the metabolite BAJ 2740-ketohydroxy caused reduced body size of Collembola juveniles at all tested doses. TERs based on reproductive NOECs and worst case initial PEC soil values are 1020-78878. These values do not exceed the proposed trigger from the EC Guidance document on Terrestrial Toxicology of <5.

Microorganisms
Neither respiration nor nitrogen mineralisation of soils treated with spirodiclofen up to 0.98 mg/kg differed from untreated soils by greater than 25% (trigger) after 42 days. Nitrogen mineralisation of soils treated with major soil metabolites at 0.45-0.84 mg/kg did not differ from untreated soils by greater than 25% after 28 days

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.

Fish
Moderate acute toxicity to Rainbow trout (96h LC50: >58.3 mg a.s./L). Chronically toxic (42d NOEC: 0.02 mg a.s./L). Moderate toxicity to Rainbow trout of the metabolite BAJ 2740-enol. All TER calculations for spirodiclofen pass the EU triggers (Acute: 100, Chronic: 10) with a buffer zone of 20 meters.

Invertebrates
Low acute toxicity to *Daphnia magna* (48h EC50: >100 mg a.s./L). Chronically toxic to *Daphnia magna* (21d NOEC: 0.0111 mg a.s./L). Low toxicity to *Daphnia magna* of the metabolite BAJ 2740-enol. All TER calculations for spirodiclofen pass the EU triggers (Acute: 100, Chronic: 10) with a buffer zone of 30 meters.

Sediment dwelling organisms
Toxic to *Chironomus riparius* larvae (28d NOEC: 0.032 mg a.s./L (spiked water)). Low toxicity of the metabolite BAJ 2740-enol. TER calculations for spirodiclofen pass the EU trigger (10) with a buffer zone of 20 meters.

Algae
Toxic to algae (96h EC50: >4.6 mg a.s./L). TER calculations for spirodiclofen pass the EU trigger (10) with a buffer zone of 3 meters.

Microcosm/Mesocosm studies
No information.

Bioconcentration
High potential for bioaccumulation. The BCF of Spirodiclofen, based on total radioactivity, was determined to be 491 L/kg for whole fish. This exceeds the trigger value of 100. However, the proposed use in orchards involves a single seasonal application, the exposure time will be relatively short, and it rapidly depurates from fish (90% clearance time of total residues is 2

days). The BCF for the metabolite BAJ 2740-enol for fish is estimated to be 71 L/kg wet weight which is below the trigger of 100.

3.3.5. Dossier quality and completeness

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

3.4. Panel 2's assessment on health

Summary of human toxicity/inherent properties

Panel 2 has reviewed the actual documentation and points out the following inherent properties of the product, the active substance and possible metabolites:

Spirodiclofen showed low acute toxicity in rats both following oral- and dermal administration and inhalation, but showed skin sensitisation properties. The Panel concludes that spirodiclofen is not considered genotoxic, even though equivocal results concerning chromosomal aberrations appeared in *in vitro* test systems.

In the sub-chronic and chronic toxicity testing, the adrenals appeared to be a target organ in all tested species where effects on organ weight and/or histopathology were observed already at low doses. In addition to the adrenals, other organs of the endocrine system including reproductive organs were affected in all species tested. Reductions of cholesterol- and triglyceride levels were observed at low doses. Increased incidences of Leydig cell adenomas and uterine adenocarcinomas were observed in exposed rats, and liver adenomas/adenocarcinomas in mice.

Generally, males seem more sensitive for adverse reproductive effects of spirodiclofen than females. This may mirror the tissue levels of spirodiclofen which was 5-15 times higher in males than in females.

In the 2-generation study in rats, dose related trends towards decreased testes and epididymides sizes in F1 males were seen when evaluated by gross pathological examinations. Decreased epididymides- and seminal vesicle weights and increased weight of prostate were seen in F0 males exposed to the lowest doses. Decreased liver weight was seen in all treatment groups.

In F1 males, dose related trends towards increased incidence of atrophy and a decreased number of spermatides per mg tissues in testes and epididymides were observed. The mid and highest dose in F1 males and at the highest dose in females, decreased levels of cholesterol and triglyceride concentrations were seen.

No teratogenic effect was found in rats or rabbits. Spirodiclofen is not considered neurotoxic in adult or developing rats.

Based on mechanistic studies, it was indicated that the steroid hormone synthesis was decreased causing increased hormone secretion at the higher levels of hormone axis (hypothalamus-pituitary-gonadal and -adrenal axes). A possible mechanism of action could be that increasing levels of pituitary hormones could be associated with hyperplasia and tumour formation in testicular tissue, and hypertrophy and vacuolization in the adrenals. The Panel concludes that spirodiclofen may have endocrine disrupting effects because it interferes with steroid hormone

synthesis *in vitro*. However, the *in vivo* data are not sufficient to make a firm conclusion on this point.

The product Envidor 240 SC
Envidor 240 SC showed low acute toxicity to rats both following oral- and dermal administration and inhalation. The product showed no irritation to skin or eye, but showed skin sensitising properties as evaluated in the guinea pig (in 20/20 animals). Envidor 240 SC is absorbed through human skin at an estimated rate of 0.6% and 7% for the concentrate and the dilution, respectively.

National norms are set as follows:
ADI – Acceptable Daily Intake
An ADI of 0.014 mg/kg bw/day is determined based on applying a 100-fold safety factor to the NOAEL of 1.38 mg/kg bw/day from the 1-year study in dogs.

AOEL - Acceptable Operator Exposure Level
An AOEL of 0.009 mg/kg bw/day is determined based on applying a 100-fold safety factor to the NOAEL of 1.38 mg/kg bw/day from the 1-year study in dogs and additionally applying a correction factor of 0.64 to account for oral absorption.

The Panel concludes that it is not necessary to establish an ARfD for spirodiclofen due to its low acute toxicity.

Metabolites and impurities – possible exposure to humans via the environment

The metabolites (M01 and BAJ2740-ketohydroxy/MA-3OH-cyclohexylester) detected in the soil/groundwater or in plants were tested for acute toxicity orally and for bacterial mutagenicity. The studies show that the metabolites have low acute toxicity, except M01 that is moderately toxic. The metabolites tested negative in bacterial mutagenicity studies.

Risk characterization of health

Health risk due to human exposure

The Panel has based their risk characterization for operators of Envidor 240 SC on the exposure- and dose-response assessments presented in section 3.3.1 by applying the risk scale described in section 3.2.

Operator, worker and bystander exposure

Operator exposure
The estimated risk for operators provided adequate use of personal protective equipment (PPE) is assessed as minimal as the estimated exposure (UK POEM) for different uses gave a maximum value of 102% of AOEL. However, because of the skin sensitising properties of Envidor 240 SC, gloves should always be used when handling the product.

Worker exposure
The risk for workers from exposure to spirodiclofen is assessed as minimal (74% of AOEL). However, because of the skin sensitising properties of Envidor 240 gloves should always be used when handling treated crops.

Bystander exposure

The risk for bystander from exposure to spirodiclofen is assessed as minimal (8-14% of AOEL).

Health risk due to residues in products for consumption
Not included in the terms of reference.

3.5. Panel 2's assessment of environment

3.5.1. Summary of the environmental fate

Panel 2 has reviewed the actual documentation and points out the following inherent properties of the product, the active substance and possible metabolites:

Spirodiclofen is rapidly degraded in soils and has a low mobility due to high soil sorption. In areas with high risk of erosion and run-off, transport of spirodiclofen sorbed to soil particles is likely to occur. Several metabolites are formed which are highly mobile but generally rapidly degraded in soils.

3.5.2. Environmental risk characterization

The risk characterization of the product's ecotoxicological effects on the terrestrial and aquatic environments made by Panel 2 is based on the exposure- and dose/response assessments presented in section 3.3.3 by applying the risk scale described in section 3.2.

Ecotoxicological effects on terrestrial organisms

The Panel concludes that there is minimal risk for toxic effects of spirodiclofen on mammals, birds, earthworms, and soil microorganisms with the proposed application regime.

For bees, standard laboratory studies show low oral and contact toxicity to adult bees. The Panel considers these studies not to be relevant based on the mode of action of spirodiclofen. Spirodiclofen is an Insect Growth Regulator (IGR) which means that it interrupts the bees' life cycle by inhibiting the development of immature stages (e.g. larvae and pupae). Several semi-field- and field experiments have documented adverse effects of spirodiclofen on bee brood development and pupal abundance at the proposed application rate. The Panel concludes that this indicates very high risk for toxic effects of spirodiclofen to bees when the substance is applied during flowering.

Both laboratory- and field studies with non-target arthropods (predatory mites) show adverse effects above the trigger value at the suggested application rate for spirodiclofen. Even though one field experiment indicated recovery within one year, the Panel considers the risk to non-target arthropods to be very high.

Ecotoxicological effects on aquatic organisms

Exposure concentrations have been estimated based on spray drift during application in orchards which is considered by the Panel to be the worst case scenario in terms of exposure. The Panel concludes that there is a minimal risk of toxic effects on aquatic organisms due to exposure to spirodiclofen with the proposed application regime, provided that a buffer zone of 30 m to surface water is applied.

3.6. Quality of the submitted documentation

Panel 2 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

4. CONCLUSION

VKMs Panel 2 concludes as following:

Both Envidor and the active substance spirodiclofen showed low acute oral -, dermal - and inhalation toxicities in animal studies, but showed skin sensitising properties. The estimated risk for operators is assessed as minimal provided adequate use of personal protective equipment.

Spirodiclofen may have endocrine disrupting effects, but the *in vivo* data are not sufficient to make a firm conclusion at this point. Adrenals and other organs of the endocrine system, including the reproductive system, are target organs for chronic toxicity of spriodiclofen. Males seem to be more sensitive than females for adverse reproductive effects of spirodiclofen. Decreased testes and epididymides sizes, testes atrophy and decreased number of sperm were seen both in the parental and subsequent generation of rats. No teratogenic effect of spirodiclofen was seen.

The disturbances in the endocrine system may account for the carcinogenic potential of spirodiclofen as evidenced by tumours in testicles, uterus and liver of animals. Spirodiclofen is not considered genotoxic. The Panel regards spirodiclofen to be carcinogenic and toxic to the reproduction in laboratory animals.

Both spirodiclofen and its metabolites are rapidly degraded in soil, but while spirodiclofen has a low mobility due to high soil sorption, its metabolites are highly mobile.

Use of Envidor with the proposed application regime implies a very high risk for adverse effects on bees and non-target arthropods due to exposure to the active substance spirodiclofen. The risk for adverse effects of spirodiclofen on other terrestrial organisms, and on aquatic organisms provided that a buffer zone of 30 m to surface water is applied, is considered to be minimal.

5. ATTACHMENT

The Norwegian Food Safety Authority’s evaluation of the documentation submitted by the applicant, following application for registration of the insecticide/acaricide Envidor 240 SC (spirodiclofen), 2010.