Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

Risk assessment of the insecticide Movento 100 SC with the active substance spirotetramat

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

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Summary

Movento 100 SC is a new insecticide containing the active substance spirotetramat. The intended use is in stone fruit, pome fruit, vegetables and ornamentals outdoors, and lettuce, tomatoes and cucumbers in greenhouses.

VKM was requested by the Norwegian Food Safety Authority to consider possible health risk for operators related to the properties of Movento 100 SC; in particular the relevance of the effects of spirotetramat on thyroid hormones, brain, thymus and body weight observed in dogs, and the reproductive effects of spirotetramat observed in rats. VKM was also asked to consider the fate and behaviour of Movento 100 SC with the active ingredient spirotetramat in the environment, and the ecotoxicological effects and risks related to its use. The risk assessment was finalized in a meeting on May 24. 2013, by VKM's Scientific Panel on Plant Protection Products.

VKM's conclusions are as follows:

Health

VKM concludes that spirotetramat shows toxic effects in dogs and rats that could be relevant for humans. Thyroid and thymus glands are target organs in the oral subchronic toxicity studies of spirotetramat in dogs, and effects are observed from 19 mg/kg bw/day (600 ppm). Decreases in circulating thyroid hormone levels were detected in all three studies carried out with dogs (28-, 90-days and 1-year) and should be considered toxicologically relevant. The opinion of the Panel is that it cannot be excluded that the observed brain dilatation in dogs is treatment-related, and relevant to humans.

Furthermore, VKM concludes that the reproductive effect observed in rats could be relevant for humans.

VKM proposes a NOAEL of 5 mg/kg bw/day (200 ppm) for spirotetramat based on a 1- year toxicity study in dogs, and a NOAEL of 100 mg/kg bw/day based on the acute neurotoxicity study in rats.

VKM supports/proposes:

- ADI: 0.05 mg/kg bw/day.
- AOEL: 0.05 mg/kg bw/day.
- AR_fD: 1 mg/kg bw/day.

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

Environment

VKM concludes that spirotetramat and its metabolites are not expected to accumulate in soil. It is not expected that spirotetramat or any of its metabolites will reach concentrations in groundwater above the threshold level of 0.1 µg/L when the formulation Movento 100 SC is applied according to the intended use.

VKM concludes that use of Movento 100 SC with the active substance spirotetramat according to the proposed application scheme in Norway represents a minimal risk of adverse effects on terrestrial mammals, birds, earthworms, and soil microorganisms. However, in-field effects on sensitive species of predatory mites in the crop cannot be excluded.

The risk of adverse effects on bees is minimal providing that spirotetramat is not used on crops during flowering or when bees are actively foraging.

For aquatic organisms in surface water, the risk is considered minimal, provided that a 5 m buffer zone to open water 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 18, 2013 for VKM to perform a risk assessment on use of the pesticide Movento 100 SC containing the active substance spirotetramat. The risk assessment was finalized in June, 2013.

Terms of reference

Movento 100 SC is a new product containing the new active substance spirotetramat. The intended use is as an insecticide in stone fruit, pome fruit, vegetables and ornamentals outdoors, and lettuce, tomatoes and cucumbers in greenhouses.

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

- The human health risk for operators related to the properties of Movento 100 SC and spirotetramat. The Panel is in particular asked to look at the following:
    - The human health relevance of the observed effects of spirotetramat on thyroid hormones, brain, thymus and body weight observed in dogs.
    - The human health relevance of the reproductive effects of spirotetramat observed in rats.
- The fate and behaviour in the environment and the ecotoxicological effects and risks with regard to the properties of Movento 100 SC and spirotetramat.

1 Background documentation

VKM's risk assessment is based on the Norwegian Food Safety Authority's evaluation of the documentation submitted by the applicant. The Norwegian Food Safety Authority publishes both their evaluation of Movento 100 SC and their final regulatory action on the registration of the pesticide product at their homepage www.Mattilsynet.no.

2 Procedure

The first three steps of the risk assessment (hazard identification, hazard characterization and assessment of exposure) are performed by the Norwegian Food Safety Authority and involve an assessment of the documentation submitted by the pesticide notifier. The resulting report on hazard identification, hazard characterization and assessment of exposure, from which the summary is included in the present document, is then reviewed by VKM. This review may result in some amendments in the original documents of both the summary and the full report issued by the Norwegian Food Safety Authority. 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 into account the uncertainties of extrapolating data from animals to humans and are compared to the operator exposure and human exposure to possible residues in food.

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

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

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

The following scale is used:

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

Moderate excess of AOEL 100-150% of the limit

The limit is not exceeded

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

2.2 ENVIRONMENTAL RISK ASSESSMENT

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

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

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

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

In the terrestrial environment, the risk for toxic effects on bees and non-target arthropods is assessed according to other criteria. Hazard quotients for oral- (HQ_O) and contact toxicity (HQ_C) are estimated for bees. HQ_O or HQ_C is the ratio between the standardized area dose of the product (g a.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)

Movento 100 SC is a new product containing the new active substance spirotetramat.

Movento 100 SC is an aqueous suspension concentrate (SC) containing 100 g/L of the active substance. The application is for use against biting and sucking insects in apple, pear, plum, cherries, white-, red-, savoy- and spring cabbage, Brussels sprouts, cauliflower, broccoli, kale, Chinese cabbage, lettuce grown in field and in greenhouse, tomatoes and cucumbers in greenhouse and ornamentals outdoors (plant nurseries and urban landscape).

Movento 100 SC belongs to the main chemical group “Inhibitors of acetyl CoA carboxylase”. This is an insecticide with contact and ingestion effect against aphids, scale insects, whiteflies, psyllids, gall midges, thrips and mites. The active ingredient spirotetramat penetrates the plant tissue (leaves) and is distributed systemically in the xylem and phloem, leading to insect death within 2 to 5 days.

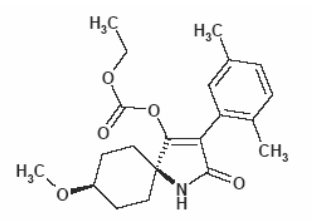
In the enclosed documentation it is noted that Movento 100 SC is gentle against beneficial organisms, including biological control agents and bees. Movento 100 SC is classified by IOBC as harmless or slightly harmful to beneficial organisms, and could be used in integrated pest management (IPM).

Pome fruit is the largest crop for use of Movento 100 SC, proposed application dose is 2250 ml Movento 100 SC/ha (225 g spirotetramat/ha), and maximal application number is two per season. Based on the product’s use in pome fruit, the standardized area dose is set to 2250 ml/ha (225 g a.s/ha), corresponding to 225 ml/daa (22,5 g a.s/daa).

3.1 IDENTITY AND PHYSICAL/CHEMICAL DATA

Product name:	Movento 100 SC
Active substance:	spirotetramat
Formulation:	Aqueous suspension concentrate (SC)
Concentration of active substance:	100 g/L
IUPAC-name:	cis-4-(ethoxycarbonyloxy)-8-methoxy-3-(2,5-xylyl)-1-azaspiro[4.5]dec-3-en-2-one
CAS number:	203313-25-1

Structural formula:



Molecular weight:	373.45 g/mol
Solubility in water:	Medium: 29.9 mg/L (20°C, pH 7)
Vapour pressure:	Low: 5.6×10^{-9} Pa (20°C, purity 99.2%)
Henrys law constant:	Low: 6.99×10^{-8} Pa m^3/mol (20°C, pH 7)
log Pow:	Medium: 2.51 (20°C, pH 7, purity 99.1%)
pKa:	10.7 (purity 99.1%)

3.2 MAMMALIAN TOXICOLOGY

3.2.1 SPIROTETRAMAT

3.2.1.1 *Toxic kinetics*

Absorption: 14C-labelled spirotetramat was readily absorbed after oral administration in all three in vivo studies. The absorption rate in rats receiving single doses of 2 or 100 mg/kg bw or repeated doses of 2 mg/kg bw for 14 days was between 89 and 98 % of the total recovered radioactivity for all dose groups. Peak plasma concentrations (Cmax) were reached within 0.09 to 2.03 hours (tmax), as calculated using pharmacokinetic modelling.

Distribution: Radioactivity was fairly equally distributed to blood, organs and tissues with preference for liver and kidneys.

Metabolism: No parent compound was detected in urine, indicating complete metabolism. Figure 5.2.1 below shows the proposed metabolic pathway of spirotetramat in rats. The main metabolic pathway is cleavage of the ester group resulting in formation of spirotetramat-enol as the primary metabolite (53-87 % of dose) from which all other metabolites could be derived. The second most prominent metabolite is spirotetramat-desmethyl-enol (5-37 %). Other downstream metabolites included spirotetramat-ketohydroxy and spirotetramat–desmethyl-ketohydroxy and also spirotetramat-enol-GA (glucuronid) and spirotetramat -enolalcohol. In male rats, the demethylation of spirotetramat-enol to spirotetramat-desmethyl-enol was higher (25-37 %) as compared to females (5-10 %).

In the high dose study (1000 mg/kg bw) in male rats, absorption and excretion were slower and lower, and radioactivity in plasma was slightly higher than in liver and kidney, as compared to the lower-dose tests. This is likely to be caused by saturation of the active transport mechanisms. Spirotetramat-enol and spirotetramat-desmethyl-enol were also in this test the primary biotransformation products, but spirotetramat-desmethyl-enol occurred at lower levels. Saturation of the active transport mechanisms in excretory organs and slow depletion and excretion of residues may potentially lead to accumulation in the body following repeated high exposure.

Results of physiologically-based pharmacokinetic (PBPK) modelling (Schmitt, 2006), considered adequate by the RMS to describe ADME behaviour of spirotetramat in male rats at doses up to 100 mg/kg bw, supports that accumulation could occur due to saturation of the renal transport process between doses of 2 to 100 mg/kg bw/day. By running the model it was assumed that the compound enters the systemic circulation as spirotetramat-enol and is further metabolised to spirotetramat -desmethyl-enol.

In vitro metabolism was studied in liver beads (immobilised hepatocytes) from male rat, mouse and humans, and showed that spirotetramat-enol was the prominent metabolite in all species (66-92 %). In mice and humans enol-glucuronide, resulting from the glucuronidation of spirotetramat-enol, was the second most prominent metabolite. However, the level of this

metabolite was five times higher in mice than in humans (30 % versus 6 %). In rats, no enol-glucuronide was detected.

Elimination: Elimination of radioactivity from tissues and organs was almost complete at the 48-hour termination in both the single and repeated dose groups, indicating that retention and accumulation of spirotetramat is unlikely (but may occur at high doses). Spirotetramat was excreted rapidly and almost completely within 24 hours, and mainly via urine. Faecal excretion accounted for 2-11 %.

3.2.1.2 *Acute toxicity*

Spirotetramat is of low acute oral or dermal toxicity and of acute inhalation toxicity (with transient signs irritation of upper airways). No classification and labelling are proposed regarding acute toxicity.

Irritation and sensitization: Spirotetramat has potential for eye irritation (rabbits, instillation into the conjunctival sac) as well as skin sensitisation (mice, Local Lymph Node Assay). The proposed classification is R36 and R43 respectively.

3.2.1.3 *Genotoxicity*

Negative results were obtained in five out of six *in vitro* and both *in vivo* assays for point mutations and chromosomal aberrations with spirotetramat. Spirotetramat was weakly positive at cytotoxic concentrations in only one *in vitro* chromosomal aberration test. Overall, the negative findings in the two *in vivo* chromosomal aberration assays and one unscheduled DNA synthesis assay in rat liver cells do not suggest a genotoxic concern for spirotetramat.

3.2.1.4 *Sub-chronic toxicity*

The insecticidal mode of action (lipid biosynthesis inhibition) was not reflected in the results of the short-term toxicological studies in rodents and dogs. Rats, mice, and dogs did not exhibit changes in plasma lipid parameters such as plasma triglycerides and plasma cholesterol.

In rats, the testis was the target organ following sub chronic oral treatment at a high dose. Abnormal spermatozoa and hypospermia in the epididymis, decreased testicular weight, and testicular degeneration and vacuolization in males were observed in males after 90 days of exposure at 10,000 ppm (616 mg/kg bw/day). These effects proved to be reversible in most animals after cessation of the treatment. Other effects in sub-chronically treated rats were limited to declines in terminal body weight in 10,000 ppm male rats and an increased incidence of accumulation of alveolar macrophages in both sexes at 10,000 ppm. Sub-chronic exposure of rats by the dermal route yielded no evidence of systemic toxicity when spirotetramat was tested up to 1000 mg/kg bw/day. This result may in part reflect the low dermal absorption (approximately 10%) in rats.

In dogs, the thyroid and thymus glands were target organs in oral sub-chronic toxicity studies. Sub-chronic exposure of spirotetramat to dogs was characterized by declines in circulating thyroid hormones. Despite a lack of correlative changes observed in thyroid weight, thyroid histopathology, or thyroid stimulating hormone, these declines are considered to be of toxicological relevance. The decline in circulating thyroid hormones may be considered as early events in the development of hypothyroidism which may be clinically manifested after exposures of longer durations. With respect to the brain dilation observed in the 1-year study

with dogs, Bayer Crop Science (BCS) has issued a position paper arguing that brain ventricle dilation has been observed in other BCS dog studies and is of hereditary origin and not treatment-related. This is also the evaluation of the USEPA. According to information in the addendum to the DAR, the observed brain dilatation is also considered as an equivocal effect by the RMS. However, when this was discussed at an EU peer review expert meeting on spirotetramat, it was concluded that, based on the concurrent control and historical control data, it cannot be excluded that it is treatment-related.

Notably, the thyroid and thymus were unaffected in rats at any dose, while testicular histopathology was not observed in dogs.

In mice, no adverse effects of any kind were observed upon testing spirotetramat orally up to the limit dose (7000 ppm).

Notable, *in vitro* results from a comparative metabolism study using hepatocytes from male rats, mice, and humans revealed species differences in the metabolism of spirotetramat. Specifically, mouse hepatocytes were better able than rat or human liver cells to metabolize spirotetramat-enol via glucuronidation. Potentially lower levels of the enol metabolite in mice in vivo may account for the lack of testicular toxicity observed in this species. However, it cannot be excluded that testicular toxicity would occur in humans, who seem to have a significantly lower rate of glucuronidation than mice.

3.2.1.5 *Chronic toxicity and carcinogenicity*

Chronic toxicity/carcinogenicity studies in rats following dietary exposure to spirotetramat for 1 and 2 years, and in mice following dietary exposure to spirotetramat for 18 months, did not reveal any treatment-related increase in tumour incidence in either sex.

In rats, target organs were kidney at medium and high doses in both sexes, and liver in females exposed to the high dose. Increased incidence of accumulation of alveolar macrophages was observed in both rat studies at medium and high dose males and high dose females. Other effects included abnormal spermatozoa or increased incidence of exfoliated germ cells in high dose male rats in both rat studies, although only statistically significant in the 2 year study.

A Functional Observational Battery assessment (motor activity, grip strength, and sensory reactivity to stimuli of different types including e.g., visual, auditory, and proprioceptive stimuli) on 10 rats/sex/dose conducted during the last month of the 1 year chronic study did not provide any indication of treatment-related neurological effects.

In mice, no adverse findings were observed up to the limit dose following long-term treatment with spirotetramat.

3.2.1.6 *Reproductive and developmental toxicity*

Reproductive toxicity and developmental toxicity of spirotetramat was investigated in a two generation study and a one generation range-finding study in rats, and in developmental studies in rat and rabbit. In addition, a supplementary developmental study in rats was performed to clarify the results of the main study.

Results of the 2-generation reproductive toxicity study in rats provided evidence of male reproductive toxicity with abnormal sperm cell morphology and effects on reproductive performance, resulting in no pregnancies at high dose. These findings were supported by results of a 1- generation range-finding study. Renal toxicity was observed in the F1-adults in

the 2-, but not the 1-generation study and offspring toxicity was observed to be limited to reduced body weights.

The applicant (BCS) has issued a position paper on *"High dose reproductive effects in male rats and their relevance to humans"* (Temerowski, 2008). In this paper, BCS argues that spirotetramat is not considered to represent a reproductive hazard to humans at the expected low dose exposure scenarios routinely generated through the agricultural use of the chemical, or even at very high dose accidental exposure. According to BCS, the testicular toxicity observed in the 2-generation rat study is not relevant for humans, as humans have the ability to conjugate spirotetramat-enol and therefore are expected to be less sensitive than rats to effects of spirotetramat on the male reproductive system. Results of the comparative *in vitro* toxicokinetic study, do indeed suggest that humans are able to conjugate spirotetramat-enol. However, this conjugation occurred to a five-times lesser extent than in mice where no reproductive toxicity was observed. To what extent a low level of this conjugation protects against reproductive effects induced by spirotetramat has not been established, and it can therefore not be concluded that testicular toxicity only occurs in species unable to conjugate spirotetramat-enol (rats). Furthermore, as pointed out by the RMS, it cannot be excluded that other metabolites can cause effects similar to those induced by spirotetramat – enol. In accordance with the RMS and conclusions made at an EU peer review expert meeting, it is therefore suggested that spirotetramat is classified as category 3 reproductive substance with R62 (Possible risk of impaired fertility).

In the developmental toxicity study in rats (Klaus 2004), offspring toxicity was observed at maternal toxicity level. In addition, increased incidences of skeletal malformations and deviations were observed at the mid and high dose. Equivocal retarded ossification was further investigated in a supplementary study and was not considered treatment related. The developmental NOAEL was set at 140 mg/kg bw/day. In accordance with the RMS and conclusions made at an EU peer review expert meeting, it is based on the increased incidences of skeletal malformations and skeletal deviations in rats at maternally toxic levels, suggested that spirotetramat is classified as category 3 reproductive substance with R63 (Possible risk of harm to the unborn child).

The developmental study in rabbit did not reveal evidence of primary embryotoxic or teratogenic potential of spirotetramat. Developmental variation and malformations were not considered treatment related and a developmental NOAEL of 160 mg/kg bw/day was suggested by the reviewer. With respect to the rabbit study, it was at the EU peer review expert meeting on spirotetramat agreed upon that the maternal NOAEL is 10 mg/kg bw per day and the developmental NOAEL is 160 mg/kg bw per day. It was also concluded that based on the available data it could not be decided whether the observed abortions (at 40 and 160 mg/kg bw/d) were due to maternal or developmental toxicity.

Two mechanistic studies to further investigate the onset of testicular toxicity in rat and the testicular toxicity of the metabolite spirotetramat-enol were carried out. The results revealed that repeated dosing is necessary to produce male reproductive effects. Based on the results of the study in rats treated with the enol-metabolite, it was concluded that reproductive toxicity is caused by either the parent compound or the enol-metabolite following enzymatic cleavage.

3.2.1.7 *Neurotoxicity*

Neurotoxicity of spirotetramat was investigated in one acute neurotoxicity study in rat. No data was available on subchronic (rat 90-day) and postnatal developmental neurotoxicity.

Clinical signs of toxicity and/or decreased motor activity were observed following a single dose of 200 mg/kg bw spirotetramat to rats. These effects were observed with greater severity at doses higher than 200 mg/kg bw in this study, as well as in a follow-up study in rats.

In the larger database, following one-year administration of spirotetramat to dogs, brain dilation with dose-related severity was observed in males at ≥ 600 ppm (20 mg/kg bw/day), while axonal degeneration in the hypothalamus was observed in one female at 1800 ppm (48 mg/kg bw/day). Clinical signs of neurotoxicity (dehydration, swelling, decreased activity and reactivity, seizures and ataxia) were also observed in one male with brain dilation at the highest dose tested. Similar effects were not observed in either rats or mice.

3.2.1.8 *Reference values*

ADI: An acceptable daily intake (ADI) of 0.05 mg/kg bw/day is suggested, based on the NOAEL of 5 mg/kg bw/day obtained in the one-year oral toxicity study in the dog and an uncertainty factor of 100.

AOEL: An acceptable operator exposure level (AOEL) of 0.05 mg/kg bw/day is suggested, based on the NOAEL of 5 mg/kg bw/day obtained in the one-year oral toxicity study in the dog and an uncertainty factor of 100

ARfD: An acute reference dose (ARfD) of 1 mg/kg bw is suggested, based on the NOAEL of 100 mg/kg bw obtained in the acute neurotoxicity study in the rat and applying an uncertainty factor of 100

3.2.1.9 *Co-formulants*

The product, Movento SC 100 / Spirotetramat SC 100 (100 g/l), contains 0.08 % of the preservative Preventol D7 (CAS no. 55965-84-9) and 0.12 % of the preservative Proxel GXL 20% (CAS no. 2634-33-5) and meets the criteria for the following risk classifications: H315, H317, H319.

3.2.2 MOVENTO SC 100

3.2.2.1 *Acute toxicity*

Acute toxicity studies on Movento SC 100 were performed with spirotetramat SC 100 G, which according to the bridging statement submitted by the applicant does not significantly differ from Movento SC 100. The formulation of Spirotetramat SC 100 G was non-toxic after acute oral and dermal administration, and induced very low inhalation toxicity (transient ungroomed hair coat in both males and females and accelerated breathing in females) to rats after nose-only administration. Hence, no classification for acute oral, dermal and inhalation toxicity is required.

3.2.2.2 *Irritation and sensitization*

Irritation and sensitisation studies on Movento SC 100 were performed with spirotetramat SC 100 G, which according to the bridging statement submitted by the applicant does not significantly differ from Movento SC 100. Spirotetramat SC 100 G was not found to be irritating to the eye and skin. However, based on a test conducted with a similar formulation expected to exhibit similar effects as Spirotetramat SC 100 G, the formulation is considered skin sensitizing and should be classified accordingly (R43 - May cause sensitisation by skin contact).

3.2.2.3 *Dermal absorption*

Dermal absorption of [14C]-Spirotetramat was investigated in one in vivo study with male rats using the OD 150 formulation, and in two in vitro studies using human and rat skin, one with the OD 150 formulation and one with the SC 240 formulation. Based on these studies and discussions at an EU peer review meeting, the following values are proposed for dermal absorption of Movento SC 100: 1% and 10 %, for the low and high dilution respectively.

3.2.2.4 *Operator exposure*

For the scenarios calculated, the results of the exposure estimations according to the UK POEM and the German model and to application in greenhouses do not exceed the proposed systemic AOEL of 0.05 mg/kg bw/d, even if no personal protective equipment (PPE) is used, with the following exceptions:

- According to the UKPOEM model (but not the German model) when used without any PPE against pest insects in apples grown in field, when applying a tractor-mounted/trailed broadcast air-assisted sprayer
- According to both the UKPOEM and German model, when used without any PPE against pest insects in apples grown in field, when applying a hand held sprayer.

Notably, no exposure operator exposure estimates exceeded the proposed systemic AOEL of spirotetramat of 0.05 mg/kg bw/d when assuming use of gloves during mixing and loading, and the use of gloves, coverall and sturdy footwear during application, in line with the skin-sensitisation potential and proposed R43 classification of spirotetramat.

3.2.2.5 *Bystanders and workers exposure*

Estimations of bystander exposure assuming PPE is used is not required since model calculations of operator exposures predict the systemic exposure of operators to be well within the acceptable exposure levels.

With respect to workers exposure, the calculated scenarios (tree fruits and ornamental assuming arms, body and legs covered, but no use of gloves); the proposed systemic AOEL is slightly exceeded for tree fruits (with a worst case assessment of the initial DFR). In line with the skin-sensitisation potential and proposed R43 classification of spirotetramat the use of gloves are recommended.

3.2.3 RESIDUES IN FOOD OR FEED

Residues are not discussed in this report.

3.3 ENVIRONMENTAL FATE AND ECOTOXICOLOGICAL EFFECTS

3.3.1 ENVIRONMENTAL FATE AND BEHAVIOUR

3.3.1.1 *Degradation in soil*

Spirotetramat is rapidly hydrolysed to spirotetramat-enol (max occurrence set to 100% of AR). Spirotetramat-enol is oxidised to spirotetramat-ketohydroxy (max occurrence 24% of AR), which is hydrolytically opened and transformed into spirotetramat-MA-amide (max

occurrence 5.2% of AR). The mineralisation of spirotetramat-MA-amide into CO_2 concludes this primary pathway.

The aerobic rate of degradation of spirotetramat is characterised as very high with DT50 0.10–0.30 days (geometric mean 0.20 days), DT90: 0.34-1.26 days. Spirotetramat-enol also degrades very quickly, but with pronounced biphasic kinetics. The DT50 is 0.02-0.18 days (geo. mean 0.05 days), DT90: 11-41 days. Spirotetramat-ketohydroxy had a medium to high degradation rate with normalised DT50 values ranging from 1.5 to 14 days (geo. mean 4.5 days), DT90: 5.1-56 days. Degradation of spirotetramat-MA-amide was fast with normalised DT50 values ranging from 0.3-4.6 days (geo. mean 1.2 days), DT90 from 1.0-28 days. The soil photolysis metabolite 4-methoxy-cyclohexanone degraded very quickly with a DT50 < 1 day.

Non-extractable residues (NER) formed in amounts of 22-35 % of applied radioactivity (AR) in the spirotetramat study (by 1-3 days) and barely declined after this. In the spirotetramat-enol study, formation of NER was even more pronounced with NER occurring at 4.2-28 % at 0 days. The plateau concentration was reached after 1 day, ranging from 40-60 % of AR. Until study termination, NER did not decrease significantly. The majority of the NER was found in the fulvic acid fraction.

Mineralisation was relatively high in both the spirotetramat and spirotetramat-enol studies. CO_2 formation was between 9.7 and 19 % of AR in the spirotetramat degradation study, while CO_2 formation was even higher in the spirotetramat-enol study, ranging from 17 to 43 % of AR.

The anaerobic primary degradation route is close to identical to the aerobic degradation route. Spirotetramat degraded very quickly (DT50 < 1 day).

Photolysis is not considered an important route of degradation for spirotetramat in soil.

The field dissipation of unlabelled spirotetramat and its metabolites was studied in four US field trials in New York, Florida, California and Washington. These studies were not considered relevant for Norwegian conditions. Spirotetramat degraded fast with a dissipation half-life of 0.3-1.0 days (geometric mean 0.7 days) and DT90 values 1.1-3.5 days. Spirotetramat-enol and spirotetramat-ketohydroxy were the main metabolites. The quantification of metabolite residues was compromised by the instability of spirotetramat-enol during storage, and no DT50 values for the individual metabolites could be estimated.

3.3.1.2 *Sorption/mobility*

The sorption of spirotetramat can be classified as medium with Kf: 3.70-4.79 L/kg (arithmetic mean 4.08 L/kg) and Kfoc: 159-435 L/kg (arithmetic mean 281 L/kg). The sorption of spirotetramat-ketohydroxy can be classified as moderate with Kf: 0.51-2.21 L/kg (arithmetic mean 1.04 L/kg) and Kfoc: 41.0-99.1 L/kg (arithmetic mean 63.7 L/kg). The sorption of spirotetramat-MA-amide can be classified as low with Kf: 0.06-0.18 L/kg (arithmetic mean 0.11 L/kg) and Kfoc: 4.4-25.5 L/kg (arithmetic mean 9.3 L/kg). The sorption of spirotetramat-enol had to be studied in a column leaching study. The Koc values derived from the column leaching study represents the first and rapidly degrading phase. The sorption can be classified as moderate with Koc: 27-99 L/kg (arithmetic mean 55 L/kg)

3.3.1.3 *Degradation in water*

The rate of hydrolysis depended strongly on pH and on temperature. At 25 °C the DT50 values of spirotetramat were 32.5, 8.6 and 0.32 days at pH 4, 7 and 9, respectively. As temperature decreased, degradation rates decreased. The major degradation product was

spirotetramat-enol, which was shown to be hydrolytically stable in the same range of temperatures and pH.

Aqueous photolysis can be considered to be an important degradation pathway for spirotetramat. In a sterilised buffer solution (pH 5), spirotetramat degraded quickly with a half-life of 2.7 days (corresponds to a DT50 of 20.2 days during natural summer light conditions). In the dark control DT50 was 26.2 days. In natural water (pH 7.9) the DT50 was found to be 0.19 days. In the dark control DT50 was 1.5 days. The major transformation products in the natural sterilised water were methoxy-cyclohexyl-aminocarboxylic acid (11.3 % AR) and methoxy-cyclohexanone (17.5 % AR). The main hydrolysis product spirotetramat-enol was also formed.

Spirotetramat is not readily biodegradable.

Aerobic water / sediment studies were conducted in two different test systems. For spirotetramat, the degradation in the whole system can be classified as very high (DT50 < 1 day). The maximum amount in sediment was 3.2 % of AR after 1 day. The major metabolites were spirotetramat-enol (max 99 % of AR) and spirotetramat-ketohydroxy (max 51% of AR). Spirotetramat-enol was shown to degrade slower in aquatic systems than in soil systems, degrading at a medium rate (whole system DT50 38 and 59 days). The distribution was max 79 % of AR in water after 7 days and 37 % of AR in sediment after 60 days. Spirotetramat-ketohydroxy was stable in both of the studied systems. The distribution after 120 days was max 13% of AR in water and 28 % of AR in sediment. The maximum formation of non-extractable residues (NER) was above 30 % of AR in both systems (max 36 % of AR). The mineralisation varied between the systems, but was relatively high, ranging from 5.9 to 24 % of AR.

3.3.1.4 *Fate in air*

Calculations using the Atkinson method estimate DT50 in the troposphere of 1.7 hours for both spirotetramat and spirotetramat-enol, while a DT50 of 4.3 hours was estimated for 4-methoxy-cyclohexanone and 2.8 hours for 4-methoxy-cyclohexyl-aminocarboxylic acid (assumes 12-hour day and 1.5 × 106 OH- cm-3). Spirotetramat has a vapour pressure of 5.6 × 10-9 Pa at 20°C, and thus has a low volatility. No significant transfer to the atmosphere is expected.

3.3.2 ENVIRONMENTAL EXPOSURE

3.3.2.1 *Soil*

According to a simple model recommended by the EU working group FOCUS the highest expected initial concentration (PIEC, predicted initial environmental concentration) in soil will be as follows for spirotetramat, spirotetramat-enol, spirotetramat-ketohydroxy and 4-methoxy-cyclohexanone, respectively: 0.,1, 0.084, 0.032 and 0.003 mg/kg (75 g/ha on bare soil in ornamentals returns the highest concentrations). Due to the fast degradation of spirotetramat and its metabolites, no accumulation in soil is expected.

3.3.2.2 *Groundwater*

Metabolites considered relevant in groundwater are spirotetramat-enol, spirotetramat-ketohydroxy, spirotetramat-MA-amide and 4-methoxy-cyclohexanone (the latter from soil photolysis). All nine EU FOCUS scenarios were modelled. Results were reported as the 80 percentile concentration at 1 m depth over 20 years. Concentrations were below 0.001 µg/L for all scenarios. Hence, it is not expected that spirotetramat or any of its metabolites will

reach concentrations above the threshold level of 0.1 µg/L when the formulation Movento 100 SC is applied according to the intended use.

3.3.2.3 *Surface water*

Models developed by EU's working group FOCUS estimate predicted environmental concentrations in surface water and sediment for different scenarios. PECsw values have been calculated for the use in pome and stone fruit (application 2 x 225 g a.s./ha) and leafy vegetables (2 x75 g a.s./ha) up to Step 2 (Northern EU). The highest PEC values resulted from the application in pome and stone fruit with PECsw of 11.79, 12.72, 6.33, 1.09 and 0.94 µg/L for spirotetramat, spirotetramat-enol, spirotetramat-ketohydroxy, 4-methoxy-cyclohexanone and 4-methoxy-cyclohexyl-aminocarboxylic acid, respectively. The corresponding PECsed values were 6.6, 6.35, 3.93, 0.03 and 0.09 µg/kg. Spray drift is assumed to be the main route of entry. As no Step 3 calculations were presented, the Norwegian Food Safety Authority considered a 5 m drift buffer for spirotetramat. This resulted in a PECsw value of 6.3 µg/L.

3.3.3 EFFECTS ON TERRESTRIAL ORGANISMS

Where there are indications that the plant protection product is more toxic than what can be explained by the content of active substance (or studies are conducted only 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 SANCO (2002). The EU triggers (birds and mammals) are >10 and >5 for TERacute and TERchronic, respectively.

3.3.3.1 *Mammals*

Low acute toxicity (LD50 > 2000 mg/kg bw/d)- In a rat multigenerational study the reproductive NOEC was toxicity 70.7/82.5 mg/kg bw/d (m/f). TER calculations for spirotetramat pass the EU triggers based on EU Tier 1 scenarios.

3.3.3.2 *Birds*

Low acute oral toxicity (LD50 > 2000 mg/kg bw/d). NOEC from reproductive studies are 4 mg/kg bw/d. Spirotetramat passes the EU trigger values for acute exposure (TERacute >600) according to the EU screening step with an application rate of 2x225 g a.s./ha in pome fruits. TERchronic fails the EU trigger based on tier 1 calculations, but pass the trigger in a higher tier risk assessment for the insectivorous indicator species white Wagtail and Blue tit.

3.3.3.3 *Bees*

Spirotetramat shows low contact (LD50 >100 µg/bee) and oral (LD50 >107 µg/bee) toxicity to bees. Hazard quotients for contact (Qhc) and oral exposure (Qho) pass the trigger value (<50). Because of the potential effects of spirotetramat on brood development (based on the effects observed in the semi-field studies and the mode of action of spirotetramat), spirotetramat should not be used on crops during flowering or when bees are actively foraging.

3.3.3.4 *Non-target arthropods*

Extended laboratory studies on parasitoids and foliage-dwelling predators did not show effects above the trigger effect level of 50 %. Effects on predatory mites (*T. pyri*) however

exceeded the ESCORT 2 trigger of 50 % effect (mortality) at doses at and above 42 g/ha. In a field study carried out in grape vines no dose-related, statistically significant effects were observed during the study period.

3.3.3.5 *Earthworms*

Spirotetramat shows moderate acute toxicity (LC50 > 500 mg/kg d.w. soil). In a chronic toxicity study with the predominant soil metabolite spirotetramat-enol the NOEC is 32 mg/kg d.w. soil. TER calculations for spirotetramat pass the EU triggers for both acute (≥10) and chronic (≥5) toxicity.

3.3.3.6 *Other soil macro organisms*

Low acute toxicity (LD50 > 1000 mg a.s/kg d.w.soil, NOEC 316 mg a.s/kg d.w.soil). TER calculations for spirotetramat pass the EU triggers both for acute (≥10) and chronic (≥5) toxicity.

3.3.3.7 *Microorganisms*

The effect of technical spirotetramat on N- and C-transformation in soil was studied in 28-days laboratory tests in accordance with OECD Guideline 216 and 217, respectively. No significant effects above the 25% trigger were seen.

3.3.3.8 *Terrestrial plants*

Corn (Zea mays) is the most sensitive species. The intended use of Movento 100 SC in pome fruit crops will not constitute an unacceptable risk of adjacent non-target plants provided a buffer zone of 3 meters is used.

3.3.4 AQUATIC ORGANISMS

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

The TER calculations below are based on maximum PEC-values from FOCUS surface water modelling and the lowest acute (LC50 or EC50) or chronic (NOEC) values for the different organism groups. FOCUS Step 2 is calculated for all tested substances. If the TER fails the triggers, PEC values based on drift when applying different buffer zones are calculated. The EU triggers for TERacute and TERlong-term are >100 and >10, respectively. PEC and TER values for the metabolites of spirotetramat are not included below, since they all show lower toxicity than spirotetramat. Movento 100 SC does not seem to be more toxic than can be explained by the toxicity of spirotetramat.

3.3.4.1 *Fish*

Spirotetramat is acutely toxic (96h LC50: 1.96-2.59 mg a.s./L), and showed moderate chronic toxicity (28d NOEC: 0.534 mg a.s./L) to fish. Spirotetramat-enol and 4-methoxycyclohexanone showed low acute toxicity (96h LC50: >100 mg/L). Movento 100 SC showed moderate acute toxicity (96h LC50: 22.3 mg/L).

Both acute and long-term TER calculations for spirotetramat pass the EU triggers based on Step 2 calculations.

3.3.4.2 *Invertebrates*

Spirotetramat showed moderate to very high acute toxicity to invertebrates (48h EC50: 0.85->43 mg a.s./L), and low chronic toxicity (21d NOEC: 2.0 mg a.s./L) to *Daphnia magna*. Spiroteramat-enol and 4-methoxycyclohexanone showed low acute toxicity (96h LC50: >100 mg/L) to *D. magna*. No studies with Movento 100 SC have been reported. The notifier argues that daphnids are less sensitive than fish, algae and sediment-dwelling organisms.

Acute TER for use in fruit fail the EU trigger based on Step 2 calculations, but pass the trigger based on drift calculations with a 5 meter buffer zone. Long-term TER for use in fruit and both acute and long-term TER for use in vegetables pass the EU trigger based on Step 2 calculations.

3.3.4.3 *Sediment dwelling organisms*

Spirotetramat is acutely toxic (48h EC50: 1.30 mg a.s./L) and showed moderate chronic toxicity (28d NOEC: 0.1 mg a.s./L (spiked water)) to chironomid larvae. Spirotetramat-enol, spirotetramat-ketohydroxy, 4-methoxycyclohexanone and spirotetramat-cis-metoxy-cyclohexylamino carboxylic acid showed low to moderate acute toxicity (96h LC50: 75- >100 mg/L) to chironomid larvae. Movento 100 SC is acutely toxic to chironomid larvae (48h EC50: 8.63 mg/L).

Long-term TER for use in fruit fail the EU trigger based on Step 2 calculations, but pass the trigger based on drift calculations with a 5 meter buffer zone. Acute TER for use in fruit and both acute and long-term TER for use in vegetables pass the EU trigger based on Step 2 calculations.

3.3.4.4 *Aquatic plants*

Spirotetramat and spirotetramat-enol are toxic to duckweed (14d EC50: 4.6-5.4 mg a.s./L).

TER calculations for spirotetramat pass the EU triggers based on Step 2 calculations.

3.3.4.5 *Algae*

Spirotetramat showed very high toxicity to algae (72-96h EC50: 0.36-15 mg a.s./L). Spirotetramat-enol and 4-methoxycyclohexanone showed low toxicity (72h EC50: >100 mg/L) to algae. Movento 100 SC showed low toxicity to algae (72h EC50: 134 mg/L).

TER calculations for spirotetramat pass the EU triggers based on Step 2 calculations.

3.3.4.6 *Microorganisms*

Spirotetramat showed low acute toxicity to wastewater microorganisms in activated sludge (3h EC50 >10 000 mg a.s./L).

3.3.4.7 *Microcosm/Mesocosm studies*

No information.

3.3.4.8 *Bioconcentration*

No studies required for spirotetramat or the metabolites, since they all have log Pow below the trigger of 3.

3.4 DOSSIER QUALITY AND COMPLETENESS

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

4 Risk characterization

4.1 SUMMARY OF HUMAN TOXICITY/INHERENT PROPERTIES

In the terms of reference VKM was requested to consider possible health risk for operators related to the properties of the active substance spirotetramat and the product Movento 100 SC ; in particular the relevance of the effects of spirotetramat on thyroid hormones, brain, thymus and body weight observed in dogs, and the reproductive effects of spirotetramat observed in rats.

4.1.1 EFFECTS SEEN IN DOG STUDIES

VKM discussed the seriousness of the effects in studies with dogs and concluded that thyroid and thymus glands are target organs in the oral subchronic toxicity studies, and that effects could be observed from 19 mg/kg bw/day (600 ppm). Decreases in circulating thyroid hormone levels were detected in three studies, and should be considered as toxicologically relevant. Furthermore, it cannot be excluded that the observed brain dilatation could be treatment-related. Higher doses of spirotetramat also induced decreased body weights.

Thyroid and thyroid hormones: A dose–related decrease in thyroid hormones (T4 and T3) were observed in three different studies with spirotetramat, 28-days, 90-days and 1-year, both in male and female dogs. The hormonal decreases were significant from 400 ppm, 150 ppm and 200 (600) ppm, respectively, in the three studies. The T4 and T3 levels were measured at various time-points during the studies, and the onset for significant reduction of T4 and/or T3 varied. The declines in circulating thyroid hormones were observed at lower concentrations than those needed for induced changes in thyroid weight and thyroid histopathology. Reduced thyroid follicular size was noted in two dogs at 1800 ppm (equal to 55 mg/kg bw/day). Thus, it cannot be excluded that the observed decline in thyroid hormones could be an early event in the development of hypothyroidism, and should therefore be considered as toxicologically relevant.

Brain: Brain dilatation was observed in the 1-year study, and describes a condition where a brain ventricle is identified to be larger than expected. Dilated brain was observed in males at 600 (mild) and 1800 ppm (moderate), and was noted in females, but only at 600 ppm (moderate); mild axonal degeneration was also detected in one female dog at 1800 ppm. The notifier (BCS) claimed that with a persistent incidence of only one individual dog per dose group (spirotetramat study and historical controls) and since brain ventricle dilation also has been observed in other BCS dog studies, there should be valid reasons to conclude that the phenomenon represents a pre-existing condition, and thus not treatment-related. VKM concludes, however, that although brain ventricle dilation has been observed in other dog studies, it cannot be excluded that this serious response could be treatment-related.

Thymus and body weight: In addition to the thyroid, also the thymus gland is a target organ for spirotetramat in oral subchronic toxicity studies in dogs. Thymus involution was graded mild in one male at 600 ppm and moderate in one male at 1800 ppm. The thymus changes (decreased size and weight, atrophy and involution) were observed at high concentrations (600-6400 ppm) in all three dog studies (28-, 90- and 365 days). The effects on thymus should be considered toxicologically relevant.

In the subchronic toxicity studies (28 and 90-days), a decrease in body weight, body weight gain, and food consumption was observed at the highest treatment doses (from 2,500 ppm and

higher). In the 1-year study there were no compound-related effects on body weights, even at the highest concentration (1800 ppm). Thus, doses of 2,500 ppm spirotetramat and higher seem to affect the dog body weight.

4.1.2 THE EFFECTS SEEN IN RAT STUDIES

Reproductive effects: In addition to testicular histopathology observed following subchronic and chronic exposure of male rats to spirotetramat, evidence of male reproductive toxicity was provided in the 2-generation reproductive toxicity study. Abnormal sperm cells were reported in F1-generation male rats treated with 6000 ppm (419 mg/kg bw/day) spirotetramat in the diet, and decreased reproductive performance was also observed in one of these males. The findings were supported by a 1-generation range-finding study. Renal toxicity was observed in the F1-adults in the 2-, but not the 1-generation study, and offspring toxicity was observed to be limited to reduced body weights.

In an investigative study designed to explore the time of onset of testicular toxicity in rats, decreased epididymal sperm counts were recorded after more than 10 days treatment to 1000 mg/kg bw/day by gavage. Repeated dosing, therefore, seems necessary to produce male reproductive toxicity in rats. In a second investigative study of a spirotetramat metabolite, male rats were treated by gavage with the enol metabolite (formed by enzymatic cleavage of parent compound) for 21 days at a dose of 800 mg/kg bw/day. Spermatotoxicity, abnormal sperm, and Sertoli cell vacuolation were observed in the testis-epididymides of treated animals. Therefore, male reproductive toxicity in rats is likely due to the enol metabolite (or further oxidation products) of spirotetramat. The testicular toxicity was not observed in mice, probably due to the high conjugation of the enol metabolite with glucuronic acid (approximately 30%). The notifier claimed that based on a metabolic similarity between mice and humans, it is likely that humans are also less sensitive to the enol metabolite toxicity than rats. However, VKM concludes that due to the low conjugation in human liver cells at high doses (only 2%), as well as the far lower conjugation in humans compared to mice, it cannot be assumed that humans are fundamentally different from rats with regard to sensitivity to spirotetramat. Thus, VKM concludes that the reproductive effect in rats could be relevant for humans.

Neurotoxicity: Clinical signs of toxicity and decreased motor activity were observed following one single dose of 200 mg/kg bw spirotetramat to rats.

4.1.3 ESTABLISHMENT OF REFERENCE VALUES

NOAEL

VKM concludes on a NOAEL of 5 mg/kg bw/day (200 ppm) for spirotetramat based on 1-year toxicity study in dogs, and is of the opinion that the test substance-related decrease in thyroid hormone levels, thymus involution and brain dilation is relevant for humans.

Furthermore, a NOAEL of 100 mg/kg bw/day based on the acute neurotoxicity study in rats is used to establish the ARfD value.

ADI

An ADI of 0.05 mg/kg bw/day is proposed for spirotetramat based on applying a 100-fold uncertainty factor on the NOAEL of 5 mg /kg bw/day in the 1- year toxicity study in dogs. The uncertainty factor accounts for interspecies extrapolation (10X) and intraspecies variability (10X).

AOEL
An AOEL of 0.05 mg/kg bw/day is proposed for spirotetramat based on the NOAEL of 5 mg /kg bw/day determined in the 1- year toxicity study in dogs.

AR_fD
An AR_fD of 1 mg/kg bw/day is proposed for spirotetramat based on NOAEL of 100 mg/kg bw/day in the acute neurotoxicity study in rats.

4.2 HEALTH RISK CHARACTERIZATION

4.2.1 HEALTH RISK DUE TO HUMAN EXPOSURE

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

4.2.1.1 *Operator, worker and bystander exposure*

Operator exposure:

The AOEL for spirotetramat is not exceeded when applied in greenhouses, even if no personal protective equipment (PPE) is used. On fruit trees in field there is a medium excess of AOEL without PPE, but no excess with PPE (Gloves during mixing and loading, and gloves, coveralls and sturdy footwear during application).

Worker and bystander exposure:

The AOEL is slightly exceeded for fruit trees, and thus the use of gloves is recommended.

4.2.2 HEALTH RISK DUE TO RESIDUES IN PRODUCTS FOR CONSUMPTION

Not included in the terms of reference.

4.3 ENVIRONMENTAL FATE ASSESSMENT

VKM was also asked to consider the fate and behaviour of Movento 100 SC and the active ingredient spirotetramat in the environment, and the ecotoxicological effects and risks related.

4.3.1 DEGRADATION IN SOIL

Spirotetramat degrades very quickly to spirotetramat-enol in soil (DT50: 0.1 – 0.3 days). The relevant metabolites are also degraded at high to medium rates. Spirotetramat and its metabolites are not expected to accumulate in soil.

4.3.2 MOBILITY IN SOIL AND LEACHING TO GROUNDWATER

Sorption studies indicate medium sorption of spirotetramat to soil and moderate to low sorption of the main metabolites. Due to the rapid degradation in soil, no significant leaching of spirotetramat to groundwater is expected. Leaching models show concentrations of relevant metabolites below 0.001 µg/L for all FOCUS scenarios. Hence, VKM considers it unlikely that spirotetramat or any of its metabolites will reach concentrations above the threshold level of 0.1 µg/L when the formulation Movento 100 SC is applied according to the intended use.

4.3.3 SURFACE WATER CONCENTRATIONS

Surface water concentrations of spirotetramat and the relevant metabolites have been calculated using FOCUS models, step 2. Additional calculations were performed including a 5 m buffer zone. VKM considers the calculated maximum PEC values as shown in section 3.3.2 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 3.3 and using the risk scale described in section 2.2.

4.4.1 EFFECTS AND RISKS TO TERRESTRIAL ORGANISMS

VKM concludes that the risk for toxic effects of spirotetramat to mammals, birds, earthworms, and soil microorganisms is minimal with the proposed application regime.

Extended laboratory studies with non-target arthropods Movento 100 SC showed effects above the trigger of 50% mortality for one species of predatory mites (*T. pyri*) at and above application doses of 42 g/ha, while the proposed application rate is 225 g/ha. Although a field study did not show any effects on the mite fauna, VKM considers that in-field effects on sensitive species of predatory mites in the fields cannot be excluded.

The acute contact and oral toxicity of spirotetramat to adult bees is low. Transient effects on honey-bee brood were observed under worst-case scenarios in some semi-field studies. However, no adverse effects were observed in field studies and VKM concludes that the risk of adverse effects on bees is minimal providing that spirotetramat is not used on crops during flowering or when bees are actively foraging.

4.4.2 EFFECTS AND RISK TO AQUATIC ORGANISMS

VKM concludes that there is a minimal risk for toxic effects of spirotetramat to fish, aquatic plants, and algae with the proposed application regime. For invertebrates and sediment dwelling organisms, minimal risks are calculated provided that a 5 m buffer zone is used.

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 concludes that spirotetramat show toxic effects in dogs and rats that could be relevant for humans. Thyroid and thymus glands are target organs in the oral subchronic toxicity studies in dogs. Decreases in circulating thyroid hormone levels were detected in all three studies carried out with dogs (28-, 90-days and 1-year) and should be considered toxicologically relevant. It cannot be excluded that the brain dilatation observed in the 1-year dog study is treatment-related.

Furthermore, VKM concludes that the reproductive effect observed in rats should be considered relevant for humans.

VKM proposes a NOAEL of 5 mg/kg bw/day for spirotetramat based on a 1- year toxicity study in dogs, and a NOAEL of 100 mg/kg bw/day based on the acute neurotoxicity study in rats.

VKM proposes:

- ADI: 0.05 mg/kg bw/day.
- AOEL: 0.05 mg/kg bw/day.
- ARfD: 1 mg/kg bw/day.

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

5.2 ENVIRONMENT

VKM concludes that spirotetramat and its metabolites are not expected to accumulate in soil. It is not expected that spirotetramat or any of its metabolites will reach concentrations in groundwater above the threshold level of 0.1 µg/L when the formulation Movento 100 SC is applied according to the intended use.

VKM concludes that use of Movento 100 SC with the active substance spirotetramat according to the proposed application scheme in Norway represents a minimal risk of adverse effects on terrestrial mammals, birds, earthworms, and soil microorganisms. However, in-field effects on sensitive species of predatory mites in the crop cannot be excluded.

The risk of adverse effects on bees is minimal providing that spirotetramat is not used on crops during flowering or when bees are actively foraging.

For aquatic organisms in surface water, the risk is considered minimal, provided that a 5 m buffer zone to open water is used.

6 Documentation

The documentation submitted by the applicant in the process of application for registration of Movento 100 SC has been compiled and evaluated by The Norwegian Food Safety Authority (www.Mattilsynet.no).

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