



**Risk assessment of
the pesticide Coragen 20 SC
with the active substance chlorantraniliprole**

**Opinion of the Panel on pesticides,
Norwegian Scientific Committee for Food Safety
29th of June, 2010**

ISBN: 978-82-8082-419-6

SUMMARY

Coragen 20 SC is a new product in Norway containing the active substance chlorantraniliprole. It is applied for use in apples against codling moth (*Cydia pomonella*), apple fruit moth (*Argyresthia conjugella*) and free leaf living larvae. 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 of the active substance and the product. The risk assessment of the product was approved at a meeting 11th of May 2010 by VKMs Scientific Panel on Pesticides (Panel 2). VKMs Panel 2 concludes as following: The product and the active substance have low acute oral, dermal and inhalation toxicities. Both are non-irritating to the skin, and no allergenic potential by skin contact were shown. Coragen was non-irritating to the eyes, while chlorantraniliprole showed a weak irritating potential. Chlorantraniliprole is not shown to have any genotoxic or carcinogenic potential, or to be teratogenic or toxic to the reproduction of female animals. The potential for testicular toxicity of chlorantraniliprole is unclear because the study design and the limited number of young dogs (2/sex/group) do not provide basis for a firm conclusion. No particular target organ for toxicity in any species in the sub-chronic and chronic toxicity studies was seen. The observed dose- and time dependent increased degree of microvesiculation in the zona fasciculata of the adrenal cortex in male rats, is however of uncertain biological significance. All test species (rat, mice, dog) showed physiological adaptation to chlorantraniliprole administration (increased liver metabolism with induction of cytochrome P450 enzymes) which was manifested as increased liver weight and hepatocellular hypertrophy. In the chronic toxicity study in mice, the increased liver weight and hepatocellular hypertrophy was accompanied with eosinophilic foci, which was assessed as an adverse effect. The no observed effect level (NOAEL) derived from this study serves as basis for calculations of values for acceptable daily intake (ADI) and acceptable operator exposure level (AOEL).

In Panel 2's opinion a sub-chronic study (90 days) with the technical material (E2Y45-282) including relevant concentration of the impurity IN-G2S78 should be performed. This would bring information on possible influence of the impurity on the toxicological profile of the technical material, and consequently on the assessment of the NOAELs in the various toxic studies.

The estimated risk for operator and for bystanders or for workers re-entering treated crops is assessed as minimal.

Chlorantraniliprole is persistent in soil with half live of about 1 year. The long half life indicates high potential for accumulation in soil after repeated use, which is confirmed by both model simulations and field studies. The Panel considers field data from the south of Europe not to be relevant for the Nordic conditions based on different climate conditions and soil properties contributing in different directions.

The Panel considers that the existing documentation is not sufficient for a firm conclusion on the use of normalised field data for modelling purposes. However, the substance is persistent and expected to accumulate in soil. The Panel concludes that there is minimal risk for toxic effects on mammals, birds, bees, and microorganisms in soil due to chlorantraniliprole exposure with the proposed exposure regime. Panel concludes that there is "very high risk" for effects on in-field non target arthropods from chlorantraniliprole exposure.

For soil living invertebrates, earthworms seem rather insensitive to chlorantraniliprole and the Panel considers the toxic effects to be minimal. Panel considers the risk for toxic effects on soil living arthropods to be high. Crustaceans and insects larvae are the aquatic organisms most sensitive to chlorantraniliprole. The Panel concludes that there is a minimal risk of toxic effects on aquatic organisms due to exposure to chlorantraniliprole with the proposed application regime provided that a buffer zone of 30 m to surface water is applied.

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.

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1. BACKGROUND

VKM is to perform risk assessments in the context of applications for registration of pesticides cf. Regulation on Pesticides § 4. The Norwegian Authority for Food Safety, National Registration Section, is responsible to review and assess the documentation submitted by the applicant. The Norwegian Authority for Food Safety takes a decision for or against registration of the product based on VKMs risk assessment, on information about the agricultural need of the product, and on the properties of alternative products already registered.

The Norwegian Authority for Food Safety requested 8th of April 2010 VKM to perform an environmental risk assessment on use of the pesticide Coragen 20 SC with the active substance chlorantraniliprole. Both the environmental and the health risk assessments of the product were approved by VKMs Panel 2 at a meeting 11th of May 2010.

2. TERMS OF REFERENCE

Terms of reference are as follows: "Coragen 20 SC is a new product in Norway containing the active substance chlorantraniliprole. The application concerns use in apples. 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 also asks for a statement on the inherent properties of the product, and a statement on the effects related to the limitations in the modeling.

The Panel is in particular asked to look at establishing NOAEL, ADI, AOEL and ARfD.

- The environmental risk with regard to the properties of the active substance and the product. The Panel is in particular asked to look at:
 - An assessment of foreign DT50 field data (8 fields, both Southern and Northern Europe) and the relevance to Norwegian field conditions.
 - An assessment of the importance of photosynthesis in fields.
 - The use of normalized field data in FOCUS ground water and FOCUS surface water. It is not common practice to normalize field data that are not relevant to Norwegian conditions, but is it acceptable if the data are representative of Norwegian conditions? This is common practice in the EU and is in line with FOCUS guidelines. The registrant used DT50 field data, adjusted by using the PEARL model, for higher tier simulations (for details, see "field dissipation"). How are these DT50 values considered by the Panel and how should they be used by the Norwegian Food Safety Authority?"

3. RISK ASSESSMENT

3.1. Background documentation

The Panels risk assessment is based on the Norwegian Authority for Food Safety's assessment (2010) of the documentation submitted by the applicant, and performed by the National Registration Section of the Norwegian Authority for Food Safety. The Norwegian Authority for Food Safety publishes both their report and their decision on the matter at <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 Authority for Food Safety and is a summary of their assessment of the documentation submitted by the applicant (2010). These three steps are reviewed by the Panel. According to the Panels scientific evaluation some adjustments may have found place both in the present document and in the report written by the Norwegian Authority for Food Safety (2010). The fourth step (risk characterization) of the risk assessment is the Panels conclusions, which is based on the three first steps.

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 exceeds AOEL, e.g. is higher than 100%, use of the products may lead to increased risk for health effects.

The following 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 fate of pesticides and their possible ecotoxicological effects 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). 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) and PEC or PIEC. Trigger values for TER, which express the acceptability of the risk for different organisms, have been defined by the EU.

In the terrestrial environment, the risk for toxic effects on bees and non-target arthropods is assessed according to other criterions. Hazard quotients for oral- (QH_O) and contact toxicity (QH_C) are estimated for bees. QH_O evt. QH_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.

Furthermore, the pesticides environmental fate with regard to persistence and runoff to surface- and groundwater is assessed. The concentrations of the pesticide in water are estimated by use of models with relevant scenarios based on EUs FOCUS-scenarios.

In case the initial TER calculations indicate a risk for effects on aquatic organisms in surface water, the effect of using buffer zones to reduce the PEC caused by spray drift is estimated. The estimates do not take dilution because of water change or depth into consideration, and are conservative. Further refinement of the calculation of PEC using models such as FOCUS step 2, 3 or 4 are used in case the initial worst case calculations results in unacceptable PEC values.

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 designated each group of organism.

The following 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 the scale above indicates.

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 Authority for Food Safety (hazard identification, hazard characterization and assessment of exposure)

Coragen 20 SC is a new product in Norway containing the active substance chlorantraniliprole. It is applied for use in apples against codling moth (*Cydia pomonella*), apple fruit moth (*Argyresthia conjugella*) and free leaf living larvae. The Norwegian Institute for Agricultural and Environmental Research (Bioforsk Plantehelse) is not recommending registration of Coragen 20 SC for use in apple against codling moth and free living caterpillars because of insufficient documentation. Because of the importance of having a pesticide against fruit moth they recommend that Coragen 20 SC is registered for use in apple against apple fruit moth even though the data supporting this registration is scarce.

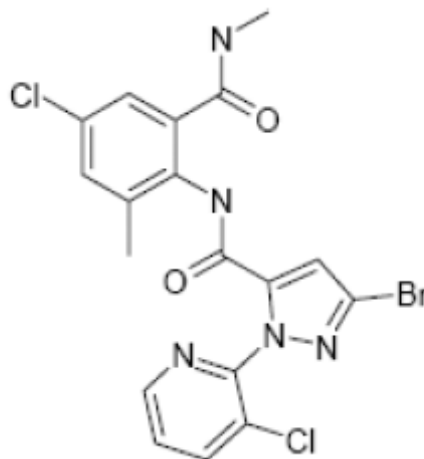
Application is before or during oviposition (mainly June). The standardized area dose is 20 ml per decare (200 ml/ha) with 75-150 litre water per decare. There should be maximum two applications with a 14 day interval. The application will be with tractor-mounted air-assisted fruit sprayer (high pressure mist blower).

Chlorantraniliprole belongs to the IRAC chemical group 28: Diamides (Ryanodine receptor modulators). The mode of action is different to most other commercial insecticides. The resistance risk is assessed to be low-moderate because of the current pest situation and the intended use of chlorantraniliprole in Norway.

3.3.1. *Identity and physical/chemical data*

Product name	Coragen 20 SC
Active substance	chlorantraniliprole
Formulation	Suspension concentrate
Concentration of active substance	200 g/l
CAS number	500008-45-7
IUPAC-name	3-bromo-4'-chloro-1-(3-chloro-2-pyridyl)-2'-methyl-6'-(methylcarbamoyl)pyrazole-5-carboxanilide

Structural formula



Molecular mass	483.15 g/mole
Solubility in water	Moderate 0.880 mg/l (20°C, pH 7)
Vapour pressure	Low 6.3×10^{-12} Pa (20°C)
Henry's constant	Low 3.2×10^{-9} Pa m ³ /mol
log Pow	Medium 2.86 (20°C, pH 7)
pKa	10.88

3.3.2. Mammalian toxicology

Chlorantraniliprole

Toxicokinetics

Absorption: Percent of dose absorbed based on biliary elimination and material balance showed 72.9-85.2 % absorption (male and female rats) in the low dose (10 mg/kg bw) compared with 11.8-13.3 % absorption (male and female rats) in the high dose (200 mg/kg bw). The absorption was based on doses recovered in bile, urine, carcasses and the GI tract tissue (excluding contents).

Distribution: The majority of the dose was initially associated with the GI tract contents and subsequently showed uptake and distribution to all tissues. The studies showed a low potential for accumulation.

Metabolism: Metabolism of the absorbed dose was extensive. The profile of the metabolites at high and low doses was similar except that a much greater portion of the administered dose was recovered as un-metabolized parent substance in the faeces in the high dose. After multiple dose administration the profile of metabolites in urine and faeces indicated extensive metabolism consistent with that observed for the single (low and high) dose study.

Excretion: Excretion in the faeces was the primary route of elimination followed by urinary excretion.

Acute toxicity

Chlorantraniliprole is of low acute toxicity by the oral, dermal and inhalation routes in the rat. It was non-irritating to the skin and minimally irritating to the eyes of the rabbits. The substance was negative in the local lymph node assay (LLNA) in the mouse and in the Magnusson-Kligman Maximization method in guinea pig.

Genotoxicity

A full battery of *in vitro* and *in vivo* genotoxicity studies was conducted with chlorantraniliprole and no indication of genotoxic potential was observed.

Subchronic and chronic toxicity

An increase in absolute and relative liver weight and hepatocellular hypertrophy was observed. These effects were considered to be adaptive due to liver metabolism with induction of cytochrome P450 enzymes and due to the absence of histomorphologic evidence of hepatocellular damage. An increased degree of microvesiculation of the adrenal cortex was observed after dermal or dietary administration of chlorantraniliprole in the rat studies. This effect is however considered non-adverse based on the lack of adverse effect on the function of the adrenal gland.

In the mouse an increase in eosinophilic foci in the liver accompanied by hepatocellular hypertrophy and increased liver weight was observed. This effect is considered adverse and is used in the determination of ADI and AOEL.

Carcinogenicity

There was no evidence of carcinogenicity in chronic studies in rats or mice.

Reproductive toxicity

No adverse effects on the reproduction parameters and no histological findings indicative of reproductive toxicity were observed. A transient reduction in pup weight under the latter half of the lactation period in the first generation was considered not adverse as the body weight was comparable to controls after weaning and the reduction in the pup weight was not repeated in the second generation.

Neurotoxicity

Chlorantraniliprole is not considered to be a neurotoxicant.

Other studies

Rats exposed to chlorantraniliprole showed a slight increase in microvesiculation in the adrenal cortex. Although clearly treatment-related, this effect is not considered adverse as it had no effect on cortical cell function as demonstrated by studies evaluating corticosterone concentrations in serum.

In immunotoxicity tests, no effects on thymus or spleen weights or on the antibody response to sheep red blood cells, were seen.

Humane data

No data reported.

Metabolites and impurities

Metabolites, identified on the plants and in the environment, were of low acute toxicity and tested negative in the Ames test.

One impurity, occurring in higher amounts in the technical material than the batches used in many toxicity studies, has a high acute toxicity (323.5 mg/kg bw). This does not affect the acute toxicity of the technical material as demonstrated by testing the technical material and showing low acute toxicity. It is however, not demonstrated that this impurity will not affect the chronic toxicity of the technical material.

The impurity was tested negative in Ames test, but in light of the identification of alert structure for genotoxicity by a model for structure-activity and its higher content in the technical material than in the toxicity tested batches, the impurity should also have been tested for genotoxicity in mammalian cells.

Coragen 20 SC

Co-formulants

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

Acute toxicity

Coragen has low acute toxicity by the oral, dermal and inhalation routes in the rat. It was non-irritating to the skin or to the eyes of the rabbits. Results of skin sensitization testing were negative in the local lymph node assay (LLNA) in the mouse.

Dermal absorption

An *in vivo* study in the rat showed a dermal absorption of 1 % for the formulated product and 7.5 % for the diluted product.

Operator, worker and bystander exposure

Operator exposure

AOEL is not exceeded even when PPE is not used.

Re-entry and bystander exposure

No re-entry activities are envisaged for the intended use. Bystander exposure is expected to be substantially less than the operator exposure. As the operator exposure without personal protective equipment is estimated to be lower than AOEL, the exposure for bystanders will be even lower.

3.3.3. Residues in food and feed

The topic is not discussed in this report.

3.3.4. Environmental fate and ecotoxicological effects

Environmental fate and behaviour

Degradation in soil

Degradation pathway: Abiotic reactions were the major transformation pathways of chlorantraniliprole and the major metabolite was IN-EQW78. Aerobic degradation: Low. DT50: 233- 886 days at 25°C, geometric mean 388 days. The degradation rate depends on temperature. The mineralization was low and the formation of bound residues was between 0.2 and 8.8 per cent. The degradation of the metabolites was low, except IN-F6L99 which is medium high. Anaerobic degradation: Low, DT50: 208 days. Photolysis in soil: Photolysis contributes to the overall degradation of the compound in soils. The DT₅₀ was calculated to be 43 days, (dark control=416 d) corresponding to a DT_{50env} of 129 sunlight equivalent days (30-50°N, 75% of midsummer peak irradiation intensity, 12 hr sunlight per day). Field dissipation: The degradation of chlorantraniliprole is moderate to low with DT50 ranging from 82 d to 611 days when exhaustive residues are used in the kinetic analyses (geomean=288 d). When conventional residues are used, shorter degradation times were observed, DT50 ranging from 63 to 247 days (geomean=144 d). DT90 was ranging from 403 to 2030 days, depending of the method of extraction. However, the DT90 values are extrapolated beyond the duration of the study and must be regarded as uncertain even though they give a certain indication

Sorption/mobility

Sorption: The sorption of chlorantraniliprole in soil can be classified as medium high with Kf: 0.6334- 9.158 (average 2.95) and Koc: 244-464 (362) and average 1/n=0.95. The adsorption was generally correlated with the % OC, % clay and clay type for the soils tests. It is a clear time dependent sorption

An aged column study indicated that the aged residues of the compound in soil have decreased mobility: Modelling with FOCUS indicated high mobility in some scenarios. Higher tier FOCUS simulations with aged kinetic sorption processes indicated acceptable mobility as regards to groundwater.

Degradation in water

Hydrolysis: Chlorantraniliprole is stable at pH 4 and 7. Photolysis: Is an important degradation pathway for Chlorantraniliprole compared to the degradation/dissipation in water. Easily degradable: The compound is not easily degradable. Water/sediment: The degradation of chlorantraniliprole for the whole system can be classified as moderate fast with DT50: 125 - 231 days (system values), geometric mean 170 days. DT90: 414-768 days. The DT90 values are extrapolated beyond the duration of the studies (100 days) and therefore they must be regarded as uncertain even though they give a certain indication. The mineralization is slow (0.15-0.53 % CO₂) and non-extractable residues in sediment after 100 days are 4.6 – 5 %.

Fate in air

Low vapour pressure and Henry's law constant indicate a low potential for volatilisation from soil under practical conditions of use. Based on these values and a estimation method developed by Lyman et al (1982) it can be predicted that < 0.01% of applied chlorantraniliprole would be lost from a treated field into the air within 24 hours.

Exposure

According to a simple model recommended by the EU working group FOCUS, PIEC (predicted initial environmental concentration) in soil was 0.05 mg/kg by application of 2x40 g active substance/ha. The calculations are based on the following assumptions: (DT50: 1378 days (worst case), 2 applications and 50 % interception). In the DAR calculated PEC_{max} was 0.278 after 20 annual applications (DT50: 1378 days and 70 % interception).

The Norwegian Food Safety Authority has used the Finnish PEC soil calculator for assessment of the potential for the accumulation. DT50 (geomean 388 days) from the laboratory study was used with application every third year (2x20 g/ha (50 % interception)). A plateau-level was never reached during 20 year. The highest concentration was 0.11 µg/l after 20 years.

Groundwater: The simulations were performed with FOCUS PELMO 3.3.2 and FOCUS PEARL 3.3.3. All the 9 FOCUS scenarios were run. Lower tier simulations indicated high mobility in some scenarios. Higher tier simulations with aged kinetic sorption processes shows $PEC_{gw} < 0.1$ µg/l. However the notifier has used DT50 from field studies and have normalised the data to pF2 and 20 °C and further they have used PEARL simulations to develop new DT50 values from these field data. It is difficult to re-examine these DT50 values.

Surface water: The transport of chlorantraniliprole and its metabolites into surface water was assessed by means of FOCUS_{sw} scenarios. The assessment started with the assumption of a worst-case loading in Step 1 and was subsequently refined in Step 1, 2, 3 and 4. All simulation runs were based on the maximum application rates of the compound in pome fruit in the EU (2x60 g a.s./ha). In Norway the maximum application rate is lower in pome fruit (2x40 g a.s./ha). Therefore, it is important to run simulations with correct application rates. In the assessment it was necessary to perform Step 4 because Step 3 runs resulted in too high PEC values when compared to effect values for some aquatic organisms. There are two kinds of additional experimental data that allow higher tier simulations at Step 4: Foliar washoff coefficient and Buffer zones. The foliar washoff coefficient (FEXTRC) was refined and the washoff behaviour was also measured for pepper and apple leaves and was in the same range as the calculated refined FEXTRC. Spray drift is the main route of entry of chlorantraniliprole in pome fruit. As a consequence different buffer widths (up to 20 m) were tested with regard to the mitigating effect on pesticide entries into the adjacent water body. The refinements were in accordance with the recommendations of FOCUS (2001). PEC_{sw} for the FOCUS scenarios R2 and D3 were: 0.24 and 0.455 µg/l and PEC_{sed} were: 0.225 and 1.08 µg/l.

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: >5000 mg/kg bw/d). TER for the indicator species in orchards is estimated as >1000. This value does not exceed the trigger. Low reproductive toxicity (NOEC: 1199 mg/kg bw/d). TER is estimated to be 885. This TER does not exceed the EU trigger of less than 10.

Birds

Low acute toxicity to birds (LD50: >2250 mg/kg bw/d). TER for the indicator species in orchards is estimated as >1000. This value does not exceed the EU trigger of less than 10. Low dietary toxicity (LC50: 1729 mg/kg bw/d). TER for the indicator species in orchards is estimated as 1433. This value does not exceed the trigger. Moderate reproductive toxicity (NOEC: 10.1 mg/kg bw/d). TER is estimated to be 8. This value does not exceed the EU trigger of less than 5.

Bees

Low contact toxicity to bees (LD50: >104 µg/bee). Toxic to bees through oral exposure (LD50: >4 µg/bee). Hazard quotients for contact (Qhc) and oral exposure (Qho) are estimated to be <0.4 and <10 respectively. These do not exceed the trigger value of more than 50.

Non-target arthropods

In Tier 1 laboratory acute contact toxicity studies, Coragen showed negligible effects on predatory mites and parasitoids. Extended lab studies did not show effects above the trigger effect level of 50%, except for a study on the larvae of the leaf dwelling predator *Episyrphus Balteatur*, where there was 100% mortality at the 4 g a.s./daa application rate. Hazard Quotients based on the lowest LR50 for *Episyrphus Balteatur* were calculated according to the ESCORT 2 guidance. The HQ for in-field is estimated to be 5.4 and exceeds the HQ trigger of 2. HQs for off-field did not exceed the HQ trigger.

Earthworms

Low acute toxicity to earthworms (LC50: >1000 mg/kg d.w. soil). TER is estimated to be 3600. This value does not exceed the EU trigger of less than 10. Low chronic toxicity (NOEC: 1000 mg/kg d.w. soil). TER is estimated to be 3600. This value does not exceed the EU trigger of less than 105).

For other soil organisms, high chronic toxicity to *F. candida* (NOEC: 0.39 mg/kg d.w. soil). TER is estimated to be 1.4. This value exceeds the proposed trigger from the EC Guidance document on Terrestrial Toxicology of less than 5, thus requiring further assessment. During the review of chlorantraniliprole in the EU, the rapporteur member state (Ireland) considered the risk to be acceptable given lack of effects in litter bag studies.

Microorganisms

Effects on microbial mediated carbon and nitrogen mineralization in soil were investigated in laboratory tests. No significant effects above the 25% trigger were seen. No effects were seen on the degradability of soil organic matter in a 12 month field litter bag study under exposure conditions simulating 10 years continual use of Coragen at an annual rate of 15 g a.s./daa.

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

Low to moderate acute toxicity (96h LC50: >12 000->15 000 µg a.s./l). Slight chronic toxicity (36-90d NOEC: 0.11-1.28 mg a.s./l). All TER calculations for chlorantraniliprole pass the EU triggers based on Step 1 or Step 2 FOCUS surface water scenarios.

Invertebrates

Very high acute toxicity to *Daphnia magna* (48h EC50: 11.6-26 µg a.s./l) and medium to very high acute toxicity to several insects and crustaceans (EC50: 11.6->1420 µg/l). High chronic toxicity to *Daphnia magna* (21d EC50: 7.16 µg a.s./l, NOEC: 4.47 µg a.s./l) and moderate chronic toxicity to Mysids (28d EC50: 840 µg a.s./l, NOEC: 695 µg a.s./l). Moderate to very high toxicity to *Daphnia magna* of five soil metabolites (IN-EQW78, IN-ECD73, IN-GAZ70, IN-F6L99 and IN-F9N04) and three water metabolites (IN-LBA22, IN-LBA23 and IN-LBA24).

Of all the tested substances, only chlorantraniliprole (both acute and chronic) and the metabolite IN-LBA23 fail the triggers based on Step 1 and Step 2 FOCUS surface water calculations. IN-LBA23 clears the trigger in Step 4 with a 10 meter buffer zone. Chlorantraniliprole fails the acute and chronic triggers at Step 4 even with a 20 meter buffer zone. Considering that all modelling is done with too high application rates, the chronic TER will pass the trigger with correct application rates. The applicant argues that the large number of tested invertebrate species could lead to a lowering of the acute TER from 100 to 10 for Step 3 and 4. If this is accepted, chlorantraniliprole passes the trigger for Step 4 with a 10 meter buffer zone.

Sediment dwelling organisms

Very high acute toxicity to *Chironomus riparius* larvae (48h EC50: 85.9 µg a.s./l) and acute toxicity to the oligochaeta *Lumbriculus variegatus* (48h EC50: >1490 µg a.s./l). High chronic toxicity to *C. riparius* larvae (28d NOEC: 5 µg a.s./kg (spiked sediment) and 2.5 µg/l (spiked water)). TER calculations for chlorantraniliprole fail the EU trigger both for the water and the sediment compartment even in Step 4 FOCUS surface water scenarios with a 20 meter buffer zone. Considering that all modelling is done with too high application rates, the TERs may pass the trigger with correct application rates and a 30 meter buffer zone.

Aquatic plants

Low to moderate toxicity to duckweed (14d EC50: >2000 µg a.s./l). TER calculations for chlorantraniliprole pass the EU trigger based on Step 1 FOCUS surface water scenarios.

Algae

Low to moderate toxicity to algae (120h EC50: >2000->15100 µg a.s./l). TER calculations for chlorantraniliprole pass the EU trigger based on Step 1 FOCUS surface water scenarios.

Microcosm/Mesocosm studies

No information.

Bioconcentration

Chlorantraniliprole shows a moderate potential for bioconcentration (BCF: 13-15) and a rapid depuration (CT50: 1.5 days, CT90: 8.9 days). Three of the soil metabolites have a high log Pow and are persistent (IN-EQW78 - log Pow 3.9, IN-ECD73 - log Pow 5.1 and IN-GAZ70 - log Pow 3.8). However, in the fish BCF study, IN-ECD73 was identified as the only major metabolite of chlorantraniliprole, and >95 % of the radioactivity at steady state depurated within two weeks. This indicates that IN-ECD73 does not have a significant potential for bioconcentration.

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

3.4.1. 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:

The product Coragen

Coragen showed low acute oral and dermal toxicity (LD 50 >5000 mg/kg bw), and low acute inhalation toxicity (LC50 >2.0 mg/L air) in rats. Furthermore, Coragen produced no erythema or oedema when applied to the skin of rabbits and no adverse effects to the eyes of the rabbit. No dermal sensitisation response of the product was seen in the local lymph node assay (LLNA) in the mouse.

Chlorantraniliprole

Chlorantraniliprole showed low acute oral and dermal toxicity (LD 50 >5000 mg/kg bw), and low acute inhalation toxicity (LC50 >5.0 mg/L air) in rats. No dermal erythma or oedema appeared after application to rabbits skin, and no corneal opacity, iritis, conjunctival redness or conjunctival chemosis were seen in the eyes of rabbits after application.

Chlorantraniliprole showed no genotoxicity in vitro or in vivo, and no carcinogenic potential.

No teratogenic potential for chlorantraniliprole was detected in rats or rabbits.

No adverse effects on the reproduction parameters and no histological findings indicative of reproductive toxicity were observed in rats. However, in the 28-days study in dogs, a dose-related decrease in testes weights (absolute weights and relative to body and brain weights) accompanied by dose-related incidences of microscopic changes were noted in young dogs. The study design and the limited number of animals (2/sex/group) does not provide basis for a firm conclusion on testicular toxicity of the substance. The finding was not reproduced in a follow-up study, in which a different batch (051) was used. The Panel concludes that the potential for testicular toxicity of chlorantraniliprole is unclear.

In the two-generation study in the rat, a transient reduction in pup weight was observed during the latter half of the lactation period in the first generation. In the Panels opinion, this is to be

considered as adverse since it was accompanied with delayed onset of puberty. The NOAEL in this study should be revised to the next highest dose (4000 ppm).

Further in the two-generation study, a slight delay in the age of perputial separation and vaginal opening was observed in the high dose group of the first generation. The Panel regards this delay in puberty onset secondary to decreased body weight at the time of weaning.

In the sub-chronic and chronic toxicity studies, increased absolute and relative liver weights with or without hepatocellular hypertrophy was observed in all test species (rat, mice, dog). These effects are probably adaptive due to increased liver metabolism with induction of cytochrome P450 enzymes. The Panel considers the increased liver weight in absence of histomorphologic evidence of hepatocellular damage not as adverse.

In the chronic mouse toxicity study (18 months), the increased liver weight and hepatocellular hypertrophy were accompanied by increased incidence of eosinophilic foci. The Panel considers this effect adverse and set a NOAEL of 158 mg/kg (male). This NOAEL is used for determination of ADI and AOEL.

In the sub-chronic and chronic toxicity studies with rats, a dose- and time dependent increased degree of microvesiculation in the zona fasciculata of the adrenal cortex was observed in males after dermal or dietary administration of chlorantraniliprole. The biological implication of this finding is uncertain. The increased degree of microvesiculation of the adrenal cortex cannot be excluded to cause some unwanted effects in animals even though not readily measurable.

No neurotoxic potential of chlorantraniliprole was revealed in the submitted studies.

National norms are set as follows:

ADI – Acceptable Daily Intake

An ADI of 1.6 mg/kg bw/day is determined based on applying a 100-fold safety factor to the NOAEL of 158 mg/kg bw/day from the 18-month feeding study in mice. Increased liver weight, hepatocellular hypertrophy and eosinophilic foci were observed at the next highest dose (935 mg/kg bw/day).

AOEL - Acceptable Operator Exposure Level

An AOEL of 0.2 mg/kg bw/day is determined based on applying a 100-fold safety factor to the NOAEL of 158 mg/kg bw/day from the 18-month feeding study in mice and additionally applying a correction factor of 0.12 to account for an oral absorption of 12 %.

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

Metabolites and impurities

Metabolites, identified on the plants and in the environment, were of low acute toxicity and tested negative in the Ames test.

One impurity, (IN-G2S78) which occurs in the final technical material, showed increased acute toxicity (323.5mg/kg, ca. 0.3%). This impurity was present in low quantity (0.05%) only in the batches used in several of the toxicity studies. Although the impurity tested negative in Ames

test, the identification of alert structure for genotoxicity by a model for structure-activity, and higher content in the relevant technical material compared to the toxicity tested batches, the impurity should be tested for genotoxicity in mammalian cells. The Panel is of the opinion that also a sub-chronic study (90 days) with the technical material (E2Y45-282) including relevant concentration of the impurity (IN-G2S78) should be performed. This would bring information on possible influence of the impurity on the toxicological profile of the technical material, and consequently on the assessment of the NOAELs in the various toxic studies.

3.4.2. Risk characterization of health

Health risk due to operator exposure:

The Panel has based their risk characterization for operators of Coragen 20 SC on the exposure- and dose-response assessments presented in section 3.3.1 and on the Norwegian Authority for Food Safety's assessment of the documentation submitted by the applicant:

Operator exposure

The estimated risk for operator is assessed as minimal since the AOEL is not exceeded even without personal protective equipment (PPE).

Worker and bystander exposure

For bystanders or for workers re-entering treated crops, the predicted exposure is expected to be substantially less than the operator exposure. The risk for bystanders and workers from exposure to chlorantraniliprole is assessed as minimal.

Health risk due to residues in products for consumption

Not included in the terms of reference

3.5. Panel 2s assessment of environment

3.5.1. Summary of the environmental fate and ecotoxicological effects

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

Chlorantraniliprole is persistent in soil with half live of about 1 year (geometric mean of 388 days in laboratory studies), and thus fulfils the persistence criterion (DT50 soil >6months) for persistent organic pollutants (POP) specified in the Stockholm convention on POPs. The long half life indicates high potential for accumulation in soil after repeated use, which is confirmed by both model simulations and field studies. However, the observed half lives in field studies are lower than those found in laboratory studies (geometric mean of 288 days), which suggests that photolysis contributes significantly to the degradation.

The Panel considers field data from the south of Europe not to be relevant for the Nordic conditions based on different climate conditions and soil properties contributing in different directions. Slow degradation in some sites is explained by soil types with high content of expanding clay minerals counting for strong sorption, but these clay types are found only in trace amounts in Norwegian agricultural soils. On the other side lower temperatures will slow down the degradation processes in the northern area, but the longer daylight in the growing season may contribute to increased photolytic degradation of the substance. The Polish field experiment may

be the most relevant for our conditions, but the way half life for the compound is calculated from this field experiment can be discussed (354 days), and could be considered to be even longer and therefore expected to accumulate.

In some cases the photolysis is expected to be important and especially close to spraying and before the compound as been transported downward the profile and protected by the soil. The Polish field experiment show that a small amount is transported downward the profile, but the main part of the compound remains in the top layer not degraded. This indicates that photolysis was of minor importance in this case.

The Panel considers that the existing documentation is not sufficient for a firm conclusion on the use of normalised field data for modelling purposes. However, the substance is persistent and expected to accumulate in soil.

3.5.2. *Environmental risk characterization*

The risk characterization of the products 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 and on the Norwegian Authority for Food Safety's assessment of the documentation submitted by the applicant:

Ecotoxicological effects on the terrestrial environment

The Panel concludes that there is minimal risk for toxic effects on mammals, birds, bees, and microorganisms in soil due to chlorantraniliprole exposure with the proposed exposure regime.

Chlorantraniliprole does not show effects above the trigger level (50%) on standard non-target arthropod species (parasitoids and predatory mites) in extended laboratory studies, but for a leaf dwelling predator, *Episyrphus balteatus*, 100% mortality was observed at the 4 g a.s./daa.

Although this is a non-standard test species, the Panel concludes that there is "very high risk" for effects on in-field non target arthropods from chlorantraniliprole exposure.

Similarly, for soil living invertebrates, earthworms seem rather insensitive to chlorantraniliprole and the Panel considers the toxic effects to be minimal, while the (non-standard) arthropod species *Folsomia candida*, a representative species for soil living arthropods, is a lot more sensitive. Despite the fact that no effects were observed in a litter bag study (12 months duration), the Panel considers the risk for toxic effects on soil living arthropods to be high.

Ecotoxicological effects on aquatic organisms

Crustaceans and insects larvae are the aquatic organisms most sensitive to chlorantraniliprole. The exposure concentrations calculated at step 4 in FOCUS with application rate 2x60 g a.s./ha and a 20 m buffer zone gives a TER = 26 for acute toxicity for aquatic invertebrates. Modified degradation rate obtained from normalization of field data have been used for calculation of the exposure concentrations, but the Panel is in doubt about the relevance of these modifications for Norwegian conditions. The modification mainly affects the surface runoff and drainage contribution while drift depends on other factors. The relative contribution of these exposure pathways is unknown. The significance with respect to exposure concentration parameters is unclear. The applicant argues that the large number of tested invertebrate species allows a lowering of the acute TER-trigger from 100 to 10. The Panel agrees that a lowering of the TER-trigger is justified, but not as much as a factor 10. The reported NOEC and EC50-values indicate

low slopes of the concentration/response slopes for some species, and a TER-trigger as low as 10 may not be sufficient to prevent acute effects on the most sensitive insect larvae. The Panel proposes that a TER trigger of 50 should be applied. Thus, the calculated TER does not fulfill this trigger even with a 20 m buffer zone. Unfortunately, the Panel has not been presented modeling results based on a lowered application rate and with larger buffer zones, but considers it most likely that the TER trigger 50 will be fulfilled with the application rate 2x40 g a.s./ha and a buffer zone of 30 m.

The Panel concludes that there is a minimal risk of toxic effects on aquatic organisms due to exposure to chlorantraniliprole with the proposed application regime provided that a buffer zone of 30 m to surface water is applied.

3.6. Quality of the back-ground documentation

Panel 2 is of the opinion that the (back-ground) documentation is adequate as a basis for an evaluation of the active substance and metabolites, but insufficient for the technical material (E2Y45-282). The impurity IN-G2S78 should be tested for genotoxic properties in mammalian cells, and a new sub-chronic study (90 days) with the technical material (E2Y45-282) including relevant concentration of the impurity IN-G2S78 should be performed. This would bring information on possible influence of the impurity on the toxicological profile of the technical material, and consequently on the assessment of the NOAELs in the various toxic studies.

4. CONCLUSION

VKMs Panel 2 concludes as following:

The product and the active substance have low acute oral, dermal and inhalation toxicities. Both are non-irritating to the skin, and no allergenic potential by skin contact were shown. Coragen was non-irritating to the eyes, while chlorantraniliprole showed a weak irritating potential.

Chlorantraniliprole is not shown to have any genotoxic or carcinogenic potential, or to be teratogenic or toxic to the reproduction of female animals. The potential for testicular toxicity of chlorantraniliprole is unclear because the study design and the limited number of young dogs (2/sex/group) do not provide basis for a firm conclusion.

No particular target organ for toxicity in any species in the sub-chronic and chronic toxicity studies was seen. The observed dose- and time dependent increased degree of microvesiculation in the zona fasciculata of the adrenal cortex in male rats, is however of uncertain biological significance.

All test species (rat, mice, dog) showed physiological adaption to chlorantraniliprole administration (increased liver metabolism with induction of cytochrome P450 enzymes) which was manifested as increased liver weight and hepatocellular hypertrophy. In the chronic toxicity study in mice, the increased liver weight and hepatocellular hypertrophy was accompanied with eosinophilic foci, which was assessed as an adverse effect. The no observed effect level (NOAEL) derived from this study serves as basis for calculations of values for acceptable daily intake (ADI) and acceptable operator exposure level (AOEL).

In Panel 2's opinion a sub-chronic study (90 days) with the technical material (E2Y45-282) including relevant concentration of the impurity IN-G2S78 should be performed. This would bring information on possible influence of the impurity on the toxicological profile of the technical material, and consequently on the assessment of the NOAELs in the various toxic studies.

The estimated risk for operator and for bystanders or for workers re-entering treated crops is assessed as minimal.

Chlorantraniliprole is persistent in soil with half live of about 1 year. The long half life indicates high potential for accumulation in soil after repeated use, which is confirmed by both model simulations and field studies.

The Panel considers field data from the south of Europe not to be relevant for the Nordic conditions based on different climate conditions and soil properties contributing in different directions.

The Panel considers that the existing documentation is not sufficient for a firm conclusion on the use of normalised field data for modelling purposes. However, the substance is persistent and expected to accumulate in soil.

The Panel concludes that there is minimal risk for toxic effects on mammals, birds, bees, and microorganisms in soil due to chlorantraniliprole exposure with the proposed exposure regime. Panel concludes that there is "very high risk" for effects on in-field non target arthropods from chlorantraniliprole exposure.

For soil living invertebrates, earthworms seem rather insensitive to chlorantraniliprole and the Panel considers the toxic effects to be minimal. Panel considers the risk for toxic effects on soil living arthropods to be high.

Crustaceans and insects larvae are the aquatic organisms most sensitive to chlorantraniliprole.

The Panel concludes that there is a minimal risk of toxic effects on aquatic organisms due to exposure to chlorantraniliprole with the proposed application regime provided that a buffer zone of 30 m to surface water is applied.

5. ATTACHMENT

The Norwegian Authority for Food Safety's assessment of the documentation for the pesticides Coragen 20 SC - chlorantraniliprole, which was submitted by the applicant in connection with the application for registration, 2010.