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Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

Risk assessment of the pesticide Centium with the active substance clomazone

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

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SUMMARY

Centium is a new product in Norway containing the active substance clomazone. The product is applied for use as a herbicide in potato, carrot, cabbage, brussel sprout, swedes, oil seed rape, pea and bean. The Norwegian Institute for Agricultural and Environmental Research recommend approval in potato, carrot, swedes and pea. They do not recommend approval in oil seed rape, cabbage and bean because of lacking documentation on efficacy. The Norwegian Scientific Committee for Food Safety (VKM) was asked by the Norwegian Food Safety Authority to perform a risk assessment on human health and environmental fate of the active substance and the product. The risk assessment of the product was finalized at a meeting May 18, 2011, by VKM's Scientific Panel on plant protection products (Panel 2). VKM Panel 2's conclusion is as follows:

The active ingredient clomazone is of moderate acute toxicity after oral and inhalation exposure and of low dermal toxicity. The product Centium is of low acute toxicity after oral exposure, by skin contact or by inhalation; however the product may contain a co-formulant, monomeric isocyanate, with sensitizing properties. Due to the lack of documentation on the monomer content, the Panel can not evaluate the risk of sensitization. UK Poem model estimation of exposure show that exposure to operator is below AOEL and the health risk is therefore minimal.

The effects observed in the dog study were considered due to the exposure of clomazone and should therefore be used to determine the NOAEL value.

The fertility index used in the two-generation study in rats is not considered relevant as a measure of critical effect. The Panel suggests to use 4000 ppm (354 mg/kg bw/day) which is the highest dose tested in the study.

Dose dependent responses were not always evident in the rat teratology study, but significant effects were found at the two highest dose levels (300 and 600 mg/kg bw/day). The observed effects were considered adverse. The proposed NOAEL of 100 mg/kg bw/day was therefore supported.

The teratology study with rats is considered relevant for determination of acute reference dose (ARfD) since skeletal malformations can be induced after short exposure periods if the exposure is taking place during a sensitive period of foetal development.

The Panel also concludes that based on the results from modeling with MACRO (4.4.2) using the Nordic groundwater scenarios and the input parameters agreed upon in the EU there is a potential for contamination of groundwater exceeding the trigger value of 0.1µg/L for the active ingredient following prescribed usage.

CONTRIBUTORS

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

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

Members of Panel 2: Line Emilie Sverdrup (Chair), Christine Bjørge, Ole Martin Eklo, Merete Grung, Torsten Källqvist, Ingeborg Klingen, Marit Låg, Edgar Rivedal, Erik Ropstad, Steinar Øvrebø.

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1. BACKGROUND

VKM performs risk assessments in the context of pesticide registration cf. Regulation on Pesticides § 4. The Norwegian Food Safety Authority, National Registration Section, is responsible for reviewing and evaluating the documentation submitted by the pesticide notifier. The Norwegian Food Safety Authority takes the final regulatory action regarding registration or deregistration of pesticides based on VKMs risk assessment, along with a comparative assessment of risk and benefits and the availability of alternatives (the principle of substitution).

The Norwegian Food Safety Authority submitted a request on April 15, 2011 for VKM to perform a risk assessment on use of the pesticide Centium 36 CS containing the active substance clomazone. Both the environmental and the health risk assessments of the product were finalized by VKM's Panel 2 at a meeting on May 18, 2011.

2. TERMS OF REFERENCE

Terms of reference as provided by the Norwegian Food Safety Authority are as follows:
"Centium 36 CS is a new herbicide in Norway containing the active substance clomazone. The application concerns use in potato, carrot, cabbage, brussels sprout, swedes, oil seed rape, pea and bean. The Norwegian Food Safety Authority would like, in this regard, an assessment of the following:

- The human health risk for operators related to the properties of the active substance and the product. The Panel is in particular asked to look at the following:
    - Establishment of NOAEL in 1-year dog study regarding adversity of the effects observed in the liver.
    - Establishment of NOAEL reproduction in two-generation study in rats related to the fertility index.
    - Evaluation the severity of the delayed skeletal ossifications and establishment of NOAEL in the rat teratology study.
    - Establishment of ARfD.
    - Assessment of the severity of 1 % isocyanate in the product regarding operator exposure.
- Fate and behaviour in the environment with regard to the properties of Centium 36 CS and clomazone".

3. RISK ASSESSMENT

3.1. Background documentation

The Panel's risk assessment is based on the Norwegian Food Safety Authority's evaluation (2011) of the documentation submitted by the applicant. The Norwegian Authority for Food Safety publishes both their evaluation of Centium and their final regulatory action on the registration of the pesticide product at their homepage: Mattilsynet

3.2. Procedure

The first three steps of the risk assessment (hazard identification, hazard characterization and assessment of exposure) are performed by the Norwegian Food Safety Authority and involve an

assessment of the documentation submitted by the pesticide notifier. The resulting summary report on hazard identification, hazard characterization and assessment of exposure, which is included in the present document, is then reviewed by VKMs Panel 2. This review may result in some amendments in the original documents of both the summary report and the full report issued by the Norwegian Food Safety Authority (2010). The fourth step (risk characterization) is based on the three first steps and is the Panel's conclusions or risk assessment.

Health risk assessment

The assessment of health risk of pesticides is based on the adverse effects produced by the active substance and product in several experimental test systems including long term animal studies. On the basis of this, limits of exposure which represent no health risk are determined. The limits take account of the uncertainties of extrapolating data for animal to human. Then the limits are compared to the operator exposure and human exposure to possible residues in food.

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 effects).

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

The following risk scale is used:

Very high risk	more than 500% of the limit
High risk	300 – 500% of the limit
Medium risk	150-300% of the limit
Moderate risk	110-150% of the limit
Minimal risk	the limit is not exceeded

The Panel may take into consideration critical co-formulants of the product when the degree of risk is to be determined. Consequently, if a product contains critical co-formulants it may be assessed to represent higher risk than what the inherent properties of active substances imply.

Environmental risk assessment

The Norwegian Food Safety Authority asked the Panel to evaluate fate and behaviour in the environment with regard to the properties of Centium 36 CS and clomazone, and the Panel was not asked to evaluate the ecotoxicological effects.

Traditionally 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.

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).

The further exposure regime in different compartment is affected on the fate of the pesticide. The fate is dependent on processes such as photodegradation, hydrolysis, biodegradation and sorption to soil particles. These processes are studied in several standardised laboratory tests. In addition, field tests are used to study the dissipation of the pesticide in various agricultural soils.

Based on the experimental fate studies, factors describing different fate processes may be derived and used in models that describe the fate of the pesticide in the soil as well as the transport to surface water and ground water. The concentrations of the pesticide in water are estimated by use of models with relevant scenarios based on EUs FOCUS-scenarios.

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

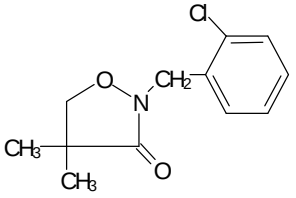
Centium 36 CS is a new product in Norway containing the new active substance clomazone. The product is applied for use as an herbicide in potato, carrot, cabbage, brussels sprout, swedes, oil seed rape, pea and bean. The Norwegian Institute for Agricultural and Environmental Research recommend approval in potato, carrot, swedes and pea. They do not recommend approval in oil seed rape, cabbage and bean because of lacking documentation on efficacy. It will be carried out more efficacy trials during the season 2011.

The standardized area dose is 0,25 l (90 g a.s.) per ha. There should be maximum one application at uses on field. The application method used for Centium is tractor-mounted sprayers.

Clomazone is a selective, systemic herbicide absorbed by roots and shoots and translocated upwards. Clomazone belong to chemical family isoxazolidinones and HRAC group F3, inhibitor of carotenoid biosynthesis. In presence of high rates of clomazone, newly developing tissue becomes white. At lower rates plant pigmentation is partly inhibited and the developing tissue may be pale green or yellow.

3.3.1. Identity and physical/chemical data

Product name	Centium 36 CS
Active substance	Clomazone
Formulation	liquid capsule suspension (CS)

Concentration of active substance	360g/L
IUPAC-name	2-(2-chlorobenzyl)-4,4-dimethyl-1,2-oxazolidin-3-one
CAS number	81777-89-1
Structural formula	
Molecular weight	239.7 g/mole
Solubility in water	Very high, 1102 mg/l (23 °C)
Vapour pressure	Medium, 1.92 x 10^{-2} Pa (20 °C)
Henrys law constant	Medium, 4.2 x 10^{-3} Pa m_3/mol
log Pow	Medium, 2,54 (23 °C)
pKa	No dissociation

3.3.2. Mammalian toxicology

Clomazone

Toxicokinetics

Absorption
Clomazone is rapidly and extensively absorbed after oral administration. Absorption rates of 87% after low dosing and up till 100% after high dosing were observed within 48 hrs based on urinary excretion and intravenous study. Peak blood concentrations were seen after 4 hours post dosing. The extent of absorption after oral administration can be considered as complete.

Distribution
Residual tissue levels detected distribution after 7 days post dosing. Residual tissue levels were very low after oral low dose (5 mg/kg b.w.) and medium dose (50 mg/kg b.w.) but higher concentrations were found after high dose (900 mg/kg b.w.). At high dose higher levels were found primarily in liver, kidney, lung, blood, hair and carcass.

Metabolism
Clomazone was almost completely metabolised, as indicated by the absence of non-metabolised parent compound and the presence of a total of 14 metabolites identified in urine or faeces. Extensive first pass metabolism seemed to take place after oral administration. The six predominant metabolites were FMC 60217, FMC 83918, FMC 87010, FMC 87009, FMC 87008

and FMC 87011 (see appendix I in the DAR). The same metabolites were found in urine and faeces, but in different concentrations. After repeated dosing the concentrations of three metabolites were significantly increased, indicating development of an enzyme inducing activity on mixed function oxidase (MFO). The metabolites were hydroxylated derivatives of the parent compound, mono-, di- and trihydroxylated metabolites, and additional metabolites were formed by oxidation and opening of the 3-isoxazolidone (heterocyclic) ring.

Elimination
The elimination of clomazone and its metabolites was fast and complete with a cumulative excretion value close to 100% after 7 days but the majority of the excretion occurred within the first two days. About 70% was excreted in urine and approximately 30% in faeces. Elimination via expired air was negligible (0.01% of administered dose). The potential for bioaccumulation of clomazone is low. The level of the parent compound found in urine and faeces was very low and metabolites were excreted as free compounds (i.e. nonconjugated) or as conjugates. The 14-day repeated dosing did not have significant influence on absorption, elimination, distribution of parent compound and metabolites in tissues. Cumulative excretion was complete within 7 days post administration, with a slight shift towards increased urinary excretion compared to the single dose group. In general some minor variances in rate and extent of absorption, biotranformation and excretion may occur which could be attributed to sex and/or size of administered dose.

Acute toxicity:
Clomazone is of moderate acute toxicity after oral and inhalation exposure and of low dermal toxicity. The proposed classification is **Xn, R20/22 Harmful by inhalation and if swallowed. (Acute Tox. 4 H332 Harmful if inhaled and Acute Tox. 4 H 302 Harmful if swallowed).**

Irritation and sensitisation:
Clomazone was not found to be neither a skin- or eye irritant nor a skin sensitiser.

Genotoxicity:
All *in vitro* and *in vivo* genotoxicity studies were negative; hence clomazone is not of genotoxic concern.

Sub-chronic toxicity:
In the short term studies, the liver was the target organ for all the species (rat, mouse and dog) with increased absolute and/or relative weight, alterations in hepatocytes (megalocytosis), and related changes in clinical chemistry parameters (elevated cholesterol levels). In a 28-day dermal study in rats, there was no evidence of adverse effects.

Chronic toxicity and carcinogenicity:
Long-term toxicity and carcinogenicity studies in rats and mice showed liver changes (increased weight, hepatocytomegaly) and persistent thymus glands (only in female mice). Clomazone is not a carcinogen in animal-studies.

Reproductive toxicity:
Two-generation study in rats showed reduced maternal body weights, maternal body weight gain and foodconsumption in parental animals in the two high dose groups. No effects were seen at the offsprings, while reduced fertility index in the high dose level was observed.

Teratology:
In the rat teratogenicity study, the maternal toxicity was manifested by a decrease in mean maternal body weight and food consumption and clinical signs. Foetal effects were a decreased body weight, and increased incidence of delayed ossifications/absence of skeletal bones and visceral abnormalities. In the rabbit teratogenicity study, there was no relevant increased incidence of malformations, developmental effects or abnormalities in foetuses. The high dose produced maternal toxicity manifested by decreased body weight, decreased or no defecation, 3 deaths, 4 abortions and some clinical signs (ataxia and red vaginal discharge).

Delayed neurotoxicity:
No studies were available for evaluation.

Special studies:
No studies were submitted.

Medical data:
No human data was available. According to occupational physicians no clinically relevant health problems associated with Clomazone production has ever been observed since the start in 1986.

Centium 36 CS

Co-formulants:
The product does contain a co-formulant which meets the criteria for **Xn; Harmful, R42 May cause sensitisation by inhalation (Resp Sens Cat.1 H334 May cause allergy or asthma symptoms or breathing difficulties if inhaled).**

Acute toxicity:
Centium 36 CS is not harmful by swallowing, skin contact or by inhalation. Hence, no classification for acute oral, dermal and inhalation toxicity is required.
Irritation and sensitisation: Centium 36 CS is neither irritating to the eye and skin nor found to be a dermal sensitiser.

Dermal absorption:
Based on the *in vitro* study with human skin the dermal absorption was 0.59% for the undiluted concentrate and 15.40% for the diluted solution.

Operator, worker and bystander exposure
UK Poem model estimate of exposure demonstrate that the operator exposure is below AOEL. Similarly, no significant levels of exposure are expected with respect to workers or bystanders. However, as a result of the hazard classification, a face shield with assisted airflow and gloves are necessary PPE to be worn during mixing and loading operations and applications, due to the risk of a coformulant that may cause sensitisation by inhalation.

3.3.3. Residues in food and feed

This is not included in this report.

3.3.4. Environmental fate and ecotoxicological effects

Degradation in soil

The initial metabolism of clomazone involves cleavage of the isoxazolidinone ring and then loss of the carbonyl carbon as CO_2. This results in the formation of a couple of short lived metabolites. Based on normalised (adjusted to 20 °C and pF 2) SFO (Single First Order) values from the six studies initially accepted by RMS the degradation rates varied between high and low, with DT50s ranging from 7 to 265 days and a geometric mean of 52 days. DT90 values range from 68 to 499 days. Excluding some of the studies, as suggested by EFSA, results in a normalised DT50 of 37 days. The amount of bound residues varied between 12 and 25 % but depending on soil moisture and temperature it could be lower. The amount of CO_2 was measured to be between 2.8 and 77 %. No metabolites were present at levels > 3.7 % of applied radioactivity (AR). There are indications that the degradation of clomazone is somewhat biphasic. At 10 °C the degradation rate is medium with DT50: 20 days and DT90: 68 days. The anaerobic degradation rate could not be calculated as there were too few time points in the study. Degradation obviously occurs though due to the fact that both CO_2 is measured in relatively high amounts after only 30 days and bound residues amount to 15 % of AR within 30 days. In addition a metabolite (FMC 65317) was identified up to 38 % of AR within the end of the study. There are no data submitted on the fate and behaviour of this metabolite. Photolysis is not an important route of degradation for clomazone in soil. The dissipation of clomazone in the field is medium to moderate in the studies assumed to be of most relevance for Norway, with DT50s of 15-74 days and a geometric mean of 43 days. DT90: 105-297 days. In general clomazone residues were only found in the upper 0-20 cm of the soil but very low concentrations were also observed as deep as 15-30 cm. Only the dissipation of clomazone was studied in the field studies submitted. There were no observations on the occurrence or dissipation of metabolites.

Sorption/mobility

The sorption of clomazone to soil can be classified as moderate to high with Kf: 1.5-7.4 (average 3.6) and Koc: 139-608 (average 287). 48 hour 1/n values varied between 0.82 and 1.00, with an average value of 0.91. Based on the amount of radioactivity in the leachate (0-2.7 %) of the different columns, fresh and aged, the degree of mobility can be classified as low to high. Clomazone was identified in the leachate of several columns.

Degradation in water

Clomazone was hydrolytically stable at 25 °C and at each pH (4.7, 7.0, 9.3) over a period of at least 6 weeks. Photolysis is not an important degradation pathway for clomazone in water. Three studies all indicate that clomazone is very slowly decomposed in water irradiated both with natural and artificial sunlight. Clomazone is not easily degradable. In a water/sediment study the degradation rate of clomazone can be classified as medium with DT50: 40-67 days (whole system), geometric mean 52 days. DT90: 139-221 days. There was hardly any mineralization of clomazone in the systems. Bound residues amounted to 3.4-15 % after 100 days. After 100 days 79 % of the applied radioactivity was still present in the water phase and of this 37 % was identified as clomazone. 7 % of AR was detected in the sediment phase after 100 days. The metabolites FMC 65317 and FMC 55657 were identified in the water phase at maximum amounts of 12-28 % of AR in both systems but there are no data submitted on these metabolites.

Fate in air
A vapour pressure of $1.92x10^{-2}$ Pa and a Henry's law constant of $4.2\ x10^{-3}$ Pa m^3 mol -1 indicate that the probability of vaporization is medium for clomazone. In a evaporation study 81 % of the applied radioactivity was recovered after 24 hours and the amount of radio-labelled volatile compounds was only 6.9 %, indicating that evaporation of clomazone from soil surfaces would not be a problem.

Exposure

PIEC (predicted initial environmental concentration) in soil after the application of 120 g active substance/ha is 0.16 mg/kg (max concentration the first year). A $PEC_{plateau}$ of about 0.46 mg/kg is reached after about 13 years of annual use.

The leaching of clomazone to groundwater at 9 European locations was modelled using the FOCUS groundwater scenarios and the pesticide leaching model FOCUS PELMO 3.3.2. Both Okehampton and Piacenza gave results above the threshold value of 0.1 µg/L. Modelling with Norwegian, Swedish end Danish scenarios using MACRO also gave results above the threshold, with the Swedish scenario Önnestad giving the highest value of 0.94 µg/l when applying clomazone in potatoes. In potatoes the simulation also was run with half the dose, but the threshold was nevertheless exceeded in some of the scenarios. The same input parameters were used in all the modelling except that 1/n was changed in one simulation to see the effect on the results. An increase in 1/n gave higher PEC values in all scenarios.

Aquatic risk assessment was conducted based on data for the active substance. PEC values in surface water were determined using the FOCUS Surface Water Tool for Exposure Predictions (Steps 1 & 2) and a maximum application rate of 120 g a.s./ha. The initial PECsw was calculated to be 0.03023 mg/L based on FOCUS Step 1. Based on FOCUS Step 2, the initial PECsw was calculated to be 0.00913 mg/L.

3.3.5 Dossier quality and completeness

The dossier is complete and adequate as a basis for 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

In the terms of reference it was stated that the panel in particular should look at the following:

- Establishment of NOAEL in 1-year dog study regarding adversity of the effects observed in the liver.
- Establishment of NOAEL reproduction in two-generation study in rats related to the fertility index.
- Evaluation of the severity of the delayed skeletal ossifications and establishment of NOAEL in the rat teratology study.
- Establishment of ARfD.
- Assessment of the severity of 1 % isocyanate in the product regarding operator exposure.

The panel discussed these points in-depth:

Establishment of NOAEL in 1-year dog study regarding adversity of the effects observed in the liver.
EFSA and the Norwegian Food Safety Authority proposed a NOAEL of 500 ppm (13.3/14.4 mg/kg bw/day in males and females respectively) based on elevated total cholesterol levels as sign of liver toxicity and organ weight changes (a/r liver weight, a/r ovary and relative brain) in the two highest dose groups. Furthermore, there was mild, transient anaemia in the high dose group following 6 month of exposure. The liver was the target organ.

The Panel considered the elevated total cholesterol levels as adverse effects. The organ weight changes are indications of effects, but there were no morphological changes upon microscopic examination of the liver. However, the Panel considered that the effects were caused by the exposure and should therefore be used in assessment of NOAEL.

Establishment of NOAEL reproduction in two-generation study in rats related to the fertility index.
Proposed NOAEL from Mattilsynet (reproduction): 2000 ppm (174 mg/kg bw/day) based on reduced fertility index in the high dose group. EFSA has proposed a NOAEL of 4000 ppm (354 mg/kg bw/day) which is the highest dose tested.

The fertility index is a measure of libido (no. animals with implantations/no. of matings x 100) and considered as an unspecific measure of reproduction, since it can be affected by many factors. It is remarkable that a reduction in the fertility index was found only in the F1”b”litter and not in the F1”a”, F2”a” and F2”b” litters. The opinion of the Panel is that the fertilty index is not relevant as a measure of critical effect in this study. This is in agreement with EFSAs proposal.

Evaluation of the severity of the delayed skeletal ossifications and establishment of NOAEL in the rat teratology study.
Proposed NOAEL (developmental): 100 mg/kg bw/day based on decreased female foetal body weight, significant increase in the incidence of foetal visceral anomalies (increased incidence of hydroureter) and in skeletal variations (delayed ossification) in the two high dose groups.

A clear dose-effect relationship was not always evident, but significant effects were found at the two highest dose levels (300 and 600 mg/kg bw/day). The observed effects occurred only in the presence of maternal toxicity. The panel considered that the observed effects can be serious for the offspring. The minor malformation and some of the indicators of delayed ossification reported were higher than the historical control values.

The Panel is asked to consider establishment of ARfD.
The Panel concludes that the teratology study with rats is relevant for determination of acute reference dose (ARfD). US-EPA has also used the same study for establishment of ARfD. The reason for this is: Skeletal malformations can be induced after short exposure periods if the exposure is during a sensitive period of foetal development.

The Panel is asked to assess the severity of 1 % isocyanate in the product regarding operator exposure.
The Panel discussed the inherent properties of isocyanate. The substance is very allergenic and can provoke asthma and allergic skin reactions as a monomer, but not as a polymer. The documentation of isocyanate in the microcapsule in the preparation is very scarce. The Norwegian Food Safety Authority has asked the manufacturer about the isocyanate in the microcapsule but the answer was not clear. They claim that the content of monomer in the product is low. Due to the lack of documentation on the monomer content the Panel can not evaluate the risk of sensitization.

National norms are set as follows:
ADI – Acceptable Daily Intake
0.133 mg/kg bw/day based on applying a 100-fold assessment factor to NOAEL of 13.3 mg clomazone/kg bw/day determined in the 1-year dog study. The target organ in long term toxicity studies is the liver, and the dog is the most sensitive species. The uncertainty factor accounts for interspecies extrapolation (10X) and intraspecies variability (10X).

AOEL - Acceptable Operator Exposure Level
0.133 mg/kg bw/day based on applying a 100-fold assessment factor to the NOAEL of 13.3 mg clomazone/kg bw determined in the 1-year dog study. In consideration of the almost complete absorption after oral uptake, 100% can be set as the level of oral absorption, thus removing the need for any correction for this aspect.

ARfD
1 mg/kg based on applying a 100-fold assessment factor to the NOAEL of 100 mg clomazone/kg bw determined in the rat teratology study.

Metabolites and impurities – possible exposure to humans via the environment
No relevant metabolites are identified.

3.4.2. Risk characterization of health

Health risk due to human exposure

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

Operator, worker and bystander exposure

Operator exposure
UK Poem model estimate of exposure indicates that the exposure of operator is below AOEL. However, as a result of the hazard classification, a face shield with assisted airflow and gloves are necessary personal protective equipment to be worn during mixing and loading operations and applications, due to the risk of a coformulant that may cause sensitisation by inhalation (R42)

Worker exposure
Centium 36 CS is applied to the soil just after planting/sowing as a pre-emergence herbicide treatment and therefore workers are not required to re-enter the field during the weeks following treatment.

Bystander exposure
In light of the application method used for Centium 36 CS (downward spray using conventional tractor mounted hydraulic sprayer), bystanders are exposed to low quantities of spray compared to operators.

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

3.5. Panel 2's assessment of environment

3.5.1. Summary of the environmental fate

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

Degradation route in soil.

In the EU evaluation process, concern has been raised on the validity of the degradation route studies due to low recoveries and lack of information, since only one study is considered as valid and acceptable as a degradation route study. Aerobic studies show minor amounts of metabolites compared to anaerobic studies where a major metabolite is detected at 37.9% AR after 60 days.

Degradation rate in soil.

On the degradation rate laboratory studies, the Rapporteur Member State (RMS) questions the validity of the originally submitted data in the degradation rate laboratory studies. Some of the degradation rate studies lack sufficient numbers of sampling dates suffers from low recovery and are performed at too high experimental temperature. Only three of nine studies were accepted by EFSA which then decided as a consequence that the longest DT50 value of 167 days was recommended for the calculations of the predicted environmental concentration (PEC). EFSA considered that the 1st order kinetics was sufficient to describe the degradation rate of clomazone (EFSA Scientific Report (2007)).

Sorption and mobility in soil.

Sorption and Kd values varies from 1.4 -7.42 which is considered to be from medium to low mobility by RMS. The Freundlich exponent (1/n) values for sorption is 0.81- 0.93, which means non-linear sorption. 1/n is a very sensitive parameter for the prediction of (PEC) and studies indicate that the mobility of clomazone is low to high in soil. By EFSA and according to FOCUS guidelines the mean value for 1/n (0.88) was selected for calculating PEC.

PEC groundwater.

The models are very sensitive to both DT50 and to 1/n as input parameters. Calculations with the EUs FOCUS-scenarios and the model PELMO show that groundwater concentrations exceeded the trigger value of 0.1µg/L in two of six scenarios in oilseed rape with yearly application. In potatoes with lower dose but with irrigation one of nine scenarios exceeded the trigger value. EFSA recommended that a second model should have been considered to calculate PEC. The model MACRO has been used by The Norwegian Food Safety Authority to simulate leaching to groundwater. Using the same input parameters as agreed upon in the EU and half of the recommended application rate (450g/ha) the trigger value was exceeded in three of the Nordic scenarios.

Degradation in water

Degradation studies of 14C-labelled clomazone in water/sediment systems showed medium primary degradation (DT50 40-67 days) but insignificant mineralisation. After 100 days 79% of the added radioactivity was found in the water phase and only 7% in the sediment. Two major metabolites were identified in the water phase.

PEC surface water.

PEC to surface water was not considered as toxicity to aquatic organisms is low

3.5.2 Environmental risk characterization

Ecotoxicological risks are not included in the terms of reference.

3.6. Quality of the submitted documentation

Panel 2 is of the opinion that the documentation submitted to VKM is adequate as a basis for an evaluation of the active substance, the metabolites, and for the technical material.

4. CONCLUSION

VKMs Panel 2 concludes as following:

The active ingredient clomazone is of moderate acute toxicity after oral and inhalation exposure and of low dermal toxicity. The product Centium is not harmful by swallowing, skin contact or by inhalation; however the product may contain a co-formulant, monomeric isocyanate, with sensitizing properties. Due to the lack of documentation on the monomer content, the Panel can not evaluate the risk of sensitization. UK Poem model estimation of exposure show that exposure to operator is below AOEL and the health risk is therefore minimal.

The effects observed in the dog study were considered due to the exposure of clomazone and should therefore be used to determine the NOAEL value.

The fertility index used in the two-generation study in rats is not considered relevant as a measure of critical effect. The Panel suggests to use 4000 ppm (354 mg/kg bw/day) which is the highest dose tested in the study.

Dose dependent responses were not always evident in the rat teratology study, but significant effects were found at the two highest dose levels (300 and 600 mg/kg bw/day). The observed effects were considered adverse. The proposed NOAEL of 100 mg/kg bw/day was therefore supported.

The teratology study with rats is considered relevant for determination of acute reference dose (ARfD) since skeletal malformations can be induced after short exposure periods if the exposure is taking place during a sensitive period of foetal development.

The Panel also concludes that based on the results from modeling with MACRO (4.4.2) using the Nordic groundwater scenarios and the input parameters agreed upon in the EU there is a potential for contamination of groundwater exceeding the trigger value of 0.1µg/L for the active ingredient following prescribed usage.

5. ATTACHMENT

The Norwegian Food Safety Authority's evaluation of the documentation submitted by the applicant, following application for registration of the herbicide Centium 36 CS (clomazone), 2011.

REFERENCES

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EU Draft Assessment Report (DAR) (Rapporteur Member State Denmark, February 2005, Corrigendum revised June 2005, December 2006, May 2007). "Clomazone, Volume 3".

Final addendum to the Draft Assessment Report (DAR) (Denmark, June 2007): "Initial risk assessment provided by the rapporteur Member State Denmark for the existing active substance Clomazone of the third stage Part A as referred to in article 8(1) of Council Directive 91/414/EEC".