Vitenskapskomiteen for mattrygghet
Norwegian Scientific Committee for Food Safety

Human health risk assessment of the pesticide Simplex with the active substances aminopyralid and fluroxypyr

Opinion of the Panel on pesticides,
Norwegian Scientific Committee for Food Safety

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SUMMARY

Simplex is a new herbicide in Norway containing the active substances aminopyralid and fluroxypyr. Aminopyralid is a new active substance in Norway, but fluroxypyr is found in several authorized products. The application concerns use in established grassland for forage, established ley and pasture and in grass at the first year of sowing. The Norwegian Scientific Committee for Food Safety (VKM) has on a request from the Norwegian Food Safety Authority performed a risk assessment on human health of the active substance and the product. The risk assessment of the product was approved at a meeting May 11 2010 by VKMs Scientific Panel on Pesticides (Panel 2). VKM's Panel 2 concludes as following:

Both Simplex and the active substance aminopyralid are characterized as extremely irritating to the eye based on persistent irritation to the eyes of rabbits. The product Simplex is also found irritating to the rabbit skin.

Aminopyralid has low acute toxicity and is not shown to have genotoxic potential, or to be teratogenic or toxic to the reproduction in animals. There may however be a carcinogenic effect of aminopyralid based on an increased number of uterine sarcomas in mice. The main target organs for sub-chronic and chronic toxicity were the caecum (rats), the stomach (dogs, inflammation) and the liver (dogs, hyperthropy). No adverse effects for chronic toxicity were seen in mice. Rabbit was the most sensitive species for toxicity and the no observed effect levels (NOAELs) derived from studies in this species serve as base for calculations of values for acceptable daily intake (ADI) and acceptable operator exposure level (AOEL).

The estimated risk for operator is assessed as minimal both by use of boom spraying (46% of AOEL) and knapsack sprayers (81% of AOEL).

However, as a result of the hazard classification, a faceshield and gloves are necessary personal protective equipment (PPE) to be worn during mixing and loading operations, due to the risk of serious damage to the eyes and skin irritation.

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 pesticides (Panel 2)

Members of Panel 2: Line Emilie Sverdrup (leader), 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 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 authorised products.

The Norwegian Authority for Food Safety requested 8th of April 2010 VKM to perform a risk assessment on health by use of the herbicide Simplex containing the two active substances aminopyralid and fluroxypyr. The risk assessment of the product was approved by VKMs Panel 2 at a meeting 11th of May 2010.

2. TERMS OF REFERENCE

Terms of reference is as follows: ”Simplex is a new herbicide in Norway containing the active substances aminopyralid and fluroxypyr. Aminopyralid is new to Norway, but fluroxypyr is found in several authorised products. The application concerns use in established grassland for forage, established ley and pasture and in grass at the first year of sawing. The Norwegian Food Safety Authority, in this regard, 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.”

3. RISK ASSESSMENT (HEALTH)

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, which is 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 conclusion, which is based on the three first steps

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 of the Norwegian conditions. The limitations of the model's estimate 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 adverse 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.

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

Simplex is a new product containing two active substances (aminopyralid and fluroxypyr), of which one of the substances (aminopyralid) is a new active substance in Norway. The intended use is as a herbicide in established grassland for forage, established ley and pasture and in grass at the first year of sowing. Bioforsk Plantehelse does not recommend use in the first year of sowing because of lack of efficacy data from the northern zone.

The Standardized Area Dose is 200 g product per decare (or 6 g aminopyralid and 20 g fluroxypyr per decare). Simplex will be used either before the first cutting (May/June) or between the first cutting and the second cutting (July/August). The application will be with tractor mounted sprayer, but in some cases it can also be relevant to use hand-held sprayer (spot spraying).

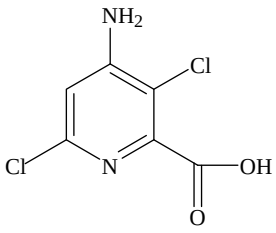
Simplex has effect against broad-leaf weeds, and will be especially important for use against creeping thistle (*Cirsium arvence*), spear thistle (*Cirsium vulgare*) and dock (*Rumex longifolius*).

Both substances in Simplex belong to the chemical group of pyridine karboxyl-acid. Because of infrequently use and influence on several action sites in the plants, there will be a low risk of development of resistance.

3.3.1. Identity and physical/chemical data

Product name	Simplex
Active substance	Aminopyralid and fluroxypyr
Formulation	Emulsion, water in oil.
Concentration of active substance	30 g aminopyralid/l and 100 g fluroxypyr/l.

Aminopyralid

IUPAC-navn	4-amino-3,6-dichloropyridine-2-carboxylic acid
CAS number	150114-71-9
Struktural formula	

Aminopyralid

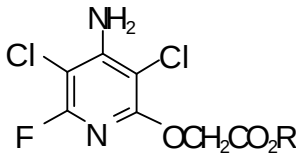
Molecular mass		207.026 g/mole
Solubility in water	Very high	205 mg/l (20°C, pH 7)
Vapour pressure	Low	9.52×10^{-9} Pa (20°C)
Henrys law constant	Low	9.61×10^{-12} Pa m^3/mol (20°C, pH 7)
log Pow	Low	-2.87 (19°C, pH 7)
pKa		2,56

Fluroxypyr meptyl

IUPAC-navn 1-methylheptyl [(4-amino-3,5-dichloro-6-fluoro-2-pyridinyl)oxy]acetate

CAS number 81406-37-3

Struktural formula



Molecular mass		367.2 g/mole
Solubility in water	Low	0.09 mg/l (20°C)
Vapour pressure	High	1.349×10^{-3} Pa (20°C)
Henrys law constant	Medium	1.06×10^{-3} Pa m^3/mol
log Pow	High	4.53
pKa		

3.3.2. *Mammalian toxicology*

Toxicokinetics

Absorption:

Aminopyralid was readily absorbed in rats and rabbits.

Rat: ca. 60% absorption within 7 days, based on urinary excretion and levels in tissues/carcass in repeated low-dose groups.

Rabbit (non-pregnant): 77% absorption within 3 days based on urinary excretion.

Rabbit (pregnant): 83-86% within 3 days based on urinary excretion.

Distribution:

Rat: Limited number of tissues was investigated. The highest concentrations were observed in skin and carcass. Low concentrations were measured in kidneys, liver and spleen.

Rabbit: Limited number of tissues was investigated. Detectable levels of the test compound were only measured in GI tract and spleen.

Rats and rabbits did not show any evidence of accumulation of the test substance.

Metabolism:

Aminopyralid was excreted unchanged indicating an absence of metabolism in rats and rabbits.

Excretion:

Rat: Aminopyralid was effectively cleared through the urine and faeces, whereas bile was not investigated.

Rabbit: Most of the administrated dose was excreted within 24 h mainly through the urine. The bile was not investigated in this study.

Acute toxicity

Aminopyralid is of low acute toxicity to the rat by the oral, dermal and inhalation routes of exposure, hence no classification is required. Aminopyralid is characterized as extremely irritating to the eye based on persisting irritation in the eyes of two of three New Zealand White rabbits (The criteria for classification as Xi; R41 “Risk of serious damage to eyes” are fulfilled), whereas it was not found to be neither a skin irritant nor a skin sensitizer.

Genotoxicity

All genotoxicity studies were negative apart from a weak positive result in an *in vitro* cytogenetic assay. The positive result at cytotoxic concentrations is not considered to be of concern because

there was a clear negative result in an *in vivo* bone marrow micronucleus assay. Overall, aminopyralid does not present a genotoxic concern according to the tests performed.

Sub-chronic toxicity

In sub-chronic toxicity studies (dietary studies), the main target organs were the caecum (only affected in rats) and the stomach (inflammation) and the liver (hyperthropy) (both only affected in dogs). No adverse effects were seen in mice. The dermal sub-chronic study in rats showed evidence of slight dermal irritation (hyperplasia) in males. The most sensitive species in sub-chronic studies is the dog.

Chronic toxicity

In chronic toxicity studies the critical effects were slight body weight decrease (males), enlarged caecum with slight mucosa hyperplasia, and urinary changes in Fisher 344 rats, whereas the critical effect observed in mice was increment in mortality of females. No progression in severity of the caecal effects was observed in the chronic study in rats compared to sub-chronic studies.

Carcinogenicity

Aminopyralid is not a carcinogen in animal-studies.

Reproductive toxicology and teratology

Reproductive toxicology: No adverse effects on reproduction parameters and no histological findings indicative of reproductive toxicity were observed.

Teratology: In high-dose rabbits, incoordinated gait was accompanied by decreased amounts of faeces, significant reductions in body weight; body weight losses, decreased body weight gains, and decreased feed consumption were observed. Those animals that died had pale kidneys, watery, dark cecal contents, erosions/ulcers of the stomach (glandular mucosa) and hairballs. No adverse effects were seen in rats.

Neurotoxicity

Aminopyralid did not result in any neurotoxic effects.

Special studies in rabbits

Transient incoordination is a consistent finding in rabbit studies with aminopyralid and aminopyralid TIPA. This finding has mostly been investigated in pregnant rabbits. Clinical observation of the behaviour of pregnant rabbits treated with high doses of aminopyralid TIPA revealed the primary abnormal finding to be incoordination of all 4 limbs. The ADME study suggests that the bioavailability of aminopyralid would be greater in late-stage pregnant rabbits than non-pregnant and early-stage pregnant rabbits. The cause of the incoordination in rabbits is

not known. In the absence of clear evidence as to the mode of action for the occurrence of incoordination in rabbits it is not possible to comment on the relevance of this hazard for humans. The precautionary approach of assuming that this effect is relevant for human hazard assessment is therefore appropriate.

Humane data
No data reported

Simplex

Co-formulants

The product does contain a co-formulant above the limit; 30% aromatic hydrocarbon solvent, thus meet the criteria for **Xi; R66 and R67.** No classification for R65 because viscosity was higher than the trigger value for the classification.

Acute toxicity

Simplex was not harmful by swallowing, skin contact or by inhalation. Hence, no classification for acute oral, dermal and inhalation toxicity is required.

Irritation and sensitization

Simplex is characterized as extremely irritating to the eye based on the irritation persisting in the eyes of two of three NZW rabbits (The criteria for classification as **Xi; R41 "Risk of serious damage to eyes"** are fulfilled). Simplex is also found irritating to the skin (the product should be classified with **X; R38/R66**) based on the persistence of desquamation in all 3 animals, whereas it was not found to be a dermal sensitizer.

Dermal absorption

No studies on dermal absorption have been conducted for either aminopyralid or fluroxypyr. The dermal absorption is not expected to be higher than the oral absorption. The higher oral absorption in the rabbit (~80%) compared to the rat (50-60%) should not be disregarded. Hence, the dermal absorption is set to 80% (both the concentration and the diluted solution) as a surrogate for a real dermal absorption value.

Operator, worker and bystander exposure

Operator exposure

UK POEM model estimate of exposure suggests that levels of exposure will be within acceptable levels for operators without PPE for application using a boom sprayer. For application with knapsack sprayers the UK POEM estimate of exposure requires gloves to be worn when handling the undiluted product during mixing and loading and during application of the diluted spray solution. However, as a result of the hazard classification, a faceshield and gloves are necessary

PPE to be worn during mixing and loading operations, due to the risk of causing serious damage to eyes (**R41**) and as the product is irritating to skin (**R38/R66**).

Worker and bystander exposure

For bystanders or for workers re-entering treated crops, predicted exposure to aminopyralid/aminopyralid potassium is less than 10% of the active substance's AOEL. The risk to bystanders and workers from exposure to aminopyralid/aminopyralid potassium is acceptable.

3.3.3. *Residues in food and feed*

This is not discussed in this report.

3.3.4. *Environmental fate and ecotoxicological effects*

This is not discussed in this report.

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 2s 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 Simplex

Simplex showed low acute oral and dermal toxicity in rats (LD 50 >5000 mg/kg bw), but is characterized as extremely irritating to the eye based on the irritation persisting in the eyes (conjunctivitis, corneal opacity and iritis) of two of three NZW rabbits. Even though only moderate occurrence of erythema and oedema was seen after application of the product to the skin of rabbits, desquamation persisted to the end of testing at day 7 which may indicate a potential of skin irritancy. Simplex was however not found to be a dermal sensitizer in guinea pigs.

Aminopyralid

Aminopyralid showed low acute oral and dermal toxicity (LD 50 >5000 mg/kg bw), and low acute inhalation toxicity (LC50 >5.5 mg/L air) in rats. It was however extremely irritating to the eye based on the persistence irritation in the eyes (conjunctivitis, corneal opacity and iritis) of two of three New Zealand White rabbits, but not a skin irritant (no erythema or edema) in rabbits or a skin sensitizer in guinea pigs.

Aminopyralid does not present a genotoxic concern according to the tests performed.

In both sub-chronic and chronic oral toxicity studies, the main target organs were the caecum (rats), the stomach (dogs, inflammation) and the liver (dogs, hyperthropy). No adverse effects were seen in mice. The dermal sub-chronic study showed slight dermal irritation (hyperplasia) in rats males.

The caecal changes in rats were characterized by dilation and hyperplasia which is assessed as an adverse effect. NOAEL 500 mg/kg bw day (rat).

In the chronic studies, body weight decrease (males), enlarged caecum with slight mucosa hyperplasia, and urinary changes were seen in rats, whereas the critical effect observed in female mice was increased mortality mainly due to nephropathy. NOAEL 50 mg/kg bw day (rat)

In the 18 month mice study, an increased number of uterine sarcomas was seen in the groups exposed to aminopyralid (0,7, 2, and 3 uterine carcinomas for the control, low-, medium- and high dose groups, respectively). Historical control data was not submitted. The Panel concludes that there may be a carcinogenic effect of aminopyralid.

Aminopyralid is assessed not to be toxic to the reproduction in rats or teratogenic in rats and rabbits.

In the teratogenic rabbit study, the maternal toxicity in the high dose group (500 mg/kg bw per day) occurred concurrently with the daily dosing and was characterized by incoordinated gait, decreased amounts of faeces, significant reductions in body weight; body weight losses, decreased body weight gains, and decreased feed consumption. In another teratogenic study, the incoordinated gait was seen in the low dose rabbits (78 mg/kg bw per day) at dosing day eight. The NOAEL from this study was 26 mg aminopyralid/kg bw per day and was used to set ADI and AOEL.

National norms are set as follows:
ADI – Acceptable Daily Intake
An ADI of 0.26 mg/kg bw/day for aminopyralid is determined based on applying a 100-fold safety factor to the NOAEL of 26 mg aminopyralid/kg bw/day in the study with pregnant rabbits.

AOEL - Acceptable Operator Exposure Level
An AOEL of 0.26 mg/kg bw/day for aminopyralid is determined based on applying a 100-fold safety factor to the NOAEL of 26 mg aminopyralid/kg bw/day for incoordination in pregnant rabbits.

The Panel concludes that no ARfD is necessary to establish due to low acute toxicity for aminopyralid.

3.4.2. Risk characterization of health

Health risk due to operator exposure:

The Panel has based their risk characterization for operators of the products 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 both by use of boom spraying (46% of AOEL) and knapsack sprayers (81% of AOEL).

However, a face shield and gloves are necessary personal protective equipment (PPE) to be worn during mixing and loading operations, due to the risk of causing serious damage to eyes and because the product is irritating to skin.

Worker and bystander exposure
For bystanders or for workers re-entering treated crops, the predicted exposure to aminopyralid/aminopyralid potassium is less than 10% of the active substance's AOEL. The risk to bystanders and workers from exposure to aminopyralid/aminopyralid potassium is assessed as minimal.

Health risk due to residues in products for consumption:

Not included in the terms of reference

3.5. 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, metabolites and technical material.

4. CONCLUSION

VKM's Panel 2 concludes as following:

Both Simplex and the active substance aminopyralid are characterized as extremely irritating to the eye based on persistent irritation to the eyes of rabbits. The product Simplex is also found irritating to the rabbit skin.

Aminopyralid has low acute toxicity and is not shown to have genotoxic potential, or to be teratogenic or toxic to the reproduction in animals. There may however be a carcinogenic effect of aminopyralid based on an increased number of uterine sarcomas in mice. The main target organs for sub-chronic and chronic toxicity were the caecum (rats), the stomach (dogs, inflammation) and the liver (dogs, hyperthropy). No adverse effects for chronic toxicity were seen in mice. Rabbit was the most sensitive species for toxicity and the no observed effect levels (NOAELs) derived from studies in this species serve as base for calculations of values for acceptable daily intake (ADI) and acceptable operator exposure level (AOEL).

The estimated risk for operator is assessed as minimal both by use of boom spraying (46% of AOEL) and knapsack sprayers (81% of AOEL).

However, as a result of the hazard classification, a faceshield and gloves are necessary personal protective equipment (PPE) to be worn during mixing and loading operations, due to the risk of serious damage to the eyes and skin irritation.

5. ATTACHMENT

The Norwegian Authority for Food Safety's assessment of the documentation for the pesticides Simplex– aminopyralid and fluroxypyr, which was submitted by the applicant in connection with the application for registration, 2010 .