

CLODINAFOF - PROPARGYL
and

CLOQUINTOCET - MEXYL



**National
Registration
Authority**

For Agricultural & Veterinary Chemicals

PUBLIC RELEASE SUMMARY

of the evaluation by the NRA of
the new active constituents:

clodinafop-propargyl
and
cloquintocet-mexyl

in the product:

TOPIK SELECTIVE HERBICIDE

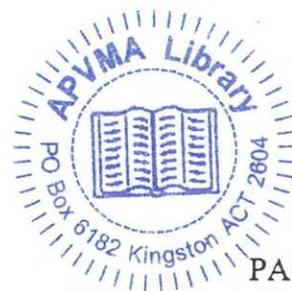
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This document is published by the National Registration Authority for Agricultural and Veterinary Chemicals. For further information, please contact -

Mr Colin Byrnes
National Registration Authority
PO Box 240
Queen Victoria Terrace
PARKES ACT 2600

Telephone: 06 272 5248
Facsimile: 06 272 3218

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FOREWORD

The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) is an independent Statutory Authority with responsibility for the assessment and approval of agricultural and veterinary chemical products prior to sale and use in Australia.

In undertaking this task, the NRA works in close cooperation with advisory agencies including the Department of Human Services and Health (Chemical Safety Unit), the Environment Protection Agency (EPA), the National Occupational Health and Safety Commission (Worksafe Australia) and State Departments of Agriculture and Health.

The NRA has a policy of encouraging openness and transparency in its activities and seeking community involvement in decision making. The publication of Public Release Summaries for all products containing new active ingredients is a part of that process.

The information and technical data required by the NRA in order to assess the safety of new chemical products and the methods of assessment must be undertaken according to accepted scientific principles. Details are outlined in the document "Interim Requirements for the Registration of Agricultural and Veterinary Chemical Products" which can be obtained from the NRA.

This Public Release Summary is intended as a brief overview of the assessment that has been completed by the NRA and advisory agencies. The document has been deliberately presented in a manner that is likely to be informative to the widest possible audience thereby encouraging public comment. More detailed technical assessment reports on occupational health and safety aspects, public health considerations, environmental impact and residues in food are available from the NRA on request.

As a relatively new organisation, the NRA welcomes comment both on the usefulness of this document and on suggestions for further improvement. Comments should be forwarded to The National Registration Manager, National Registration Authority for Agricultural and Veterinary Chemicals, PO Box 240, Queen Victoria Terrace, Parkes, ACT, 2600.

ABBREVIATIONS AND ACRONYMS WHICH MAY APPEAR IN THIS DOCUMENT

ADI	Acceptable Daily Intake (for humans)
CSU	Chemical Safety Unit (of the Department of Human Services and Health)
d	Day
EC ₅₀	Concentration at which 50% of the test population of fish are immobilised
EUP	End Use Product
F ₀	Original Parent Generation
h	Hour
HPLC	High Performance Liquid Chromatography
id	Intradermal
ip	Intraperitoneal
im	Intramuscular
iv	Intravenous
In Vitro	Outside the living body and in an artificial environment
In Vivo	Inside the living body of a plant or animal
kg	Kilogram
L	Litre
LC ₅₀	Concentration that kills 50% of the test population of organisms
LD ₅₀	Dosage of chemical that kills 50% of the test population of organisms
m	Metre
mg	Milligram
mL	Millilitre
MRL	Maximum Residue Limit (a legal limit)
MSDS	Material Safety Data Sheet
ng	Nanogram
NHMRC	National Health and Medical Research Council
NOEC/NOEL	No Observable Effect Concentration/Level
NRA	National Registration Authority for Agricultural and Veterinary Chemicals
po	Oral
ppb	parts per billion
ppm	parts per million
s	Second
sc	Subcutaneous
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
T-Value	A value used to determine the First Aid Instructions for chemical products that contain two or more poisons
TGAC	Technical Grade Active Constituent
WDG	Water Dispersible Granule
WHP	Withholding Periods

1. EXECUTIVE SUMMARY

Introduction

The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) has evaluated an application for registration of the product TOPIK SELECTIVE HERBICIDE and now invites comment from any person on that evaluation. This invitation is being made as the active constituents contained in TOPIK (*clodinafop-propargyl* and *cloquintocet-mexyl*) are new to agricultural products in Australia.

The purpose of this document is to provide a summary of the data evaluated, and of the regulatory considerations reached, during the evaluation by the NRA of TOPIK SELECTIVE HERBICIDE. The use of TOPIK is as a post-emergence herbicide to control annual grasses in wheat. Used alone, however, *clodinafop-propargyl* is not fully tolerated by small grain cereals. For this reason, the safener *cloquintocet-mexyl* has been developed to provide full crop tolerance.

Having completed its evaluation of the data submitted by the applicant in support of this use of TOPIK the NRA provides the following information for public comment:

Agricultural Aspects

TOPIK SELECTIVE HERBICIDE is for the control of important grass weed species: Wild Oats, Paradoxa Grass (or Annual Phalaris) and Annual Ryegrass in the crop: wheat.

Both *clodinafop-propargyl* and the safener *cloquintocet-mexyl* exert their activity primarily following leaf uptake. The safener selectively prevents the phytotoxic effects of *clodinafop-propargyl*.

Trials were conducted in several States of Australia which offered a wide variety of soil types, climates and conditions. The results of the trials showed that TOPIK is effective.

Environmental Aspects

Environmental exposure to *clodinafop-propargyl* and *cloquintocet-mexyl* will mainly involve the soil, as water solubility and vapour pressures are low. Laboratory and field studies indicate that both these actives and their metabolites degrade readily in soils. Accumulation, bioaccumulation and leaching are all considered unlikely.

The ecotoxicological profile of *clodinafop-propargyl* indicates low to negligible acute toxicity to birds, water fleas, algae, duckweed, bees and earthworms. Toxicity to fish is high, but the rapidly formed acid metabolite has low toxicity to fish.

The ecotoxicological profile of *cloquintocet-mexyl* indicates low to negligible acute toxicity to birds, fish, water fleas, bees and earthworms, moderate toxicity to duckweed and high toxicity to algae.

Both actives are non-persistent in the environment, and represents a low hazard to terrestrial and aquatic fauna and flora.

Toxicology

Clodinafop-propargyl, the main active ingredient in Topik Selective Herbicide, has low acute oral, dermal and inhalation toxicity, is not a skin irritant, but is a slight eye irritant and a skin sensitizer in laboratory species. *Cloquintocet-mexyl*, the other active ingredient in Topik Selective Herbicide, has low acute oral, dermal and inhalation toxicity, and is not a skin irritant, but is a slight eye irritant, and a skin sensitizer in laboratory species. Topik Selective Herbicide, the formulation containing 300 g/L *clodinafop-propargyl* and 75 g/L *cloquintocet-mexyl*, is likely to be an eye irritant and a skin sensitizer, according to the toxicological properties of the formulation components.

Clodinafop-propargyl:

The main effects of *clodinafop-propargyl* in short and long-term studies in laboratory animals were on the liver, and it was shown to act as a peroxisome proliferator in rats. Other effects included anaemia, and atrophy of the bone marrow, spleen and thymus. A long-term study in mice showed an increased incidence of benign liver tumours. A long-term study in rats showed increased incidences of tumours in the liver, prostate and ovarian tubule. Liver tumours only occurred in rats and mice at doses which produced other signs of liver damage, suggesting that they may have been secondary to liver toxicity, or peroxisome proliferation, a mechanism which is unlikely to operate in humans. These tumours occurred at doses which would greatly exceed any anticipated dietary intake, and were not considered to be a significant indicator of human health risk associated with the use of Topik Selective Herbicide.

Clodinafop-propargyl did not adversely affect reproduction, nor did it cause birth defects in laboratory species when administered during gestation, and it was not toxic to genetic material (DNA).

Cloquintocet-mexyl

Effects were only evident at high dietary levels in repeat-dose studies in laboratory animals, and included increased white blood cell numbers, anaemia, and signs of minor liver and kidney toxicity in rats. There was anaemia, increased production of red blood cells in the bone marrow and spleen, atrophy of the thymus, and decreased testes and prostate weights in dogs at 37 mg/kg bw/d. A dermal study in rats showed no effects at doses up to 1000 mg/kg bw/day. Long-term studies also showed chronic inflammation of the lining of the urinary bladder in mice, and increased cells in the thyroid follicular epithelium in female rats at 41 mg/kg bw/d and above, however there was no evidence of tumourigenicity in either species.

There was no evidence that *cloquintocet-mexyl* causes reproductive disorders or birth defects and it was not toxic to genetic material (DNA).

Conclusion

Based on an assessment of the toxicology and the potential dietary intake of residues, it was considered that there should be no adverse effects on human health from the proposed use of Topik Selective Herbicide.

Occupational Health and Safety Aspects

Clodinafop-propargyl, *cloquintocet-mexyl* and TOPIK Selective Herbicide are hazardous substances.

Clodinafop-propargyl, *cloquintocet-mexyl* and TOPIK are of low acute toxicity but have irritant and sensitising properties.

TOPIK will be formulated in Australia from imported *clodinafop-propargyl* and *cloquintocet-mexyl*. Chemical industry workers will need to be protected by engineering controls and personal protective equipment and receive adequate training.

Safety directions are established to enable end users to minimise contamination with the product. End users will need to protect the eyes and skin when handling the concentrated product. However, no specific protective clothing is considered necessary for workers applying the spray.

All workers are encouraged to maintain good occupational hygiene practices.

Clodinafop-propargyl, *cloquintocet-mexyl* and TOPIK can be used safely if handled in accordance with the control measures indicated on the *clodinafop-propargyl* and *cloquintocet-mexyl* labels, the TOPIK label and the material safety data sheets for both the active constituents and product.

Residues in Food Commodities

Residue data from Australia and overseas, using use patterns equivalent to that proposed for Australia, showed residues of the actives and their primary acid products rapidly decreased to the point of not being measurable. At the withholding period proposed for treated wheat plants, measurable residues were not found. Similarly, residues were not measurable in wheat or wheat fodder and forage. Animal transfer studies were not required because the metabolism and residue results show that it is unlikely that measurable residues would occur in animals fed with treated produce.

Trade

The studies of TOPIK indicate that residues in wheat and wheat products, and in animals fed treated wheat or wheat products, are unlikely to arise from the proposed use pattern. TOPIK is therefore deemed to present no hazard to Australia's export trade.

2. INTRODUCTION

The purpose of this document is to provide a summary of the data evaluated, and of the regulatory considerations reached, during the evaluation by the NRA of TOPIK SELECTIVE HERBICIDE. The use of TOPIK is as a post-emergence herbicide to control annual grasses in wheat. The NRA now invites comment from any person on that evaluation.

Comments should be sent to:

Mr Colin Byrnes
Manager, Agricultural Registration
National Registration Authority
PO Box 240
Queen Victoria Terrace ACT 2600
Tel: 06 272 4850
Fax: 06 272 3218

Applicant

The applicant, CIBA-GEIGY Australia Limited, has applied for the registration of TOPIK SELECTIVE HERBICIDE, a new post-emergence herbicide to control Wild Oats, Annual Ryegrass, and Paradoxa Grass or Annual Phalaris in the crop wheat

Product Details

TOPIK is formulated as an emulsifiable concentrate and contains two new active constituents: 300 g/L *clodinafop-propargyl* and 75 g/L *cloquintocet-mexyl*. TOPIK will be formulated in Australia from imported active constituents.

Overseas Registration Status

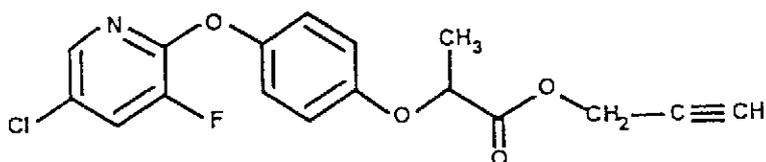
A list of countries having registrations of formulated products containing clodinafop-propargyl and cloquintocet-mexyl is provided at Annex 1.

3. PROPERTIES OF THE CHEMICAL ACTIVE CONSTITUENTS

The chemical active constituents clodinafop-propargyl and cloquintocet-mexyl are manufactured in Switzerland and have the following properties:

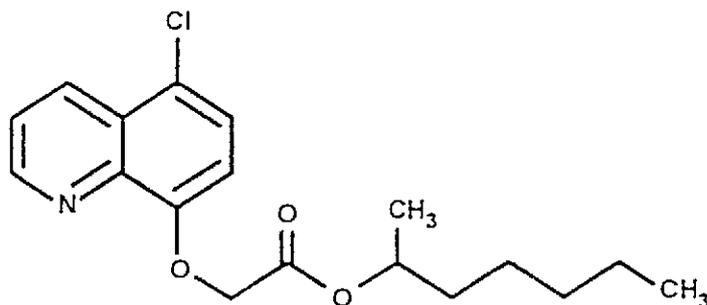
Clodinafop-propargyl:

Common name:	clodinafop-propargyl
Chemical name:	(R)-2-[4-(5-chloro-3-fluoro-2-pyridyloxy)-phenoxy]-propionic acid
Product name:	TOPIK SELECTIVE HERBICIDE
CAS Registry Number	105512-06-9
Molecular formula:	$C_{17}H_{13}ClFNO_4$
Molecular weight:	349.75
Appearance (colour):	cream
Odour:	odourless
Physical state:	fine powder
Relative density:	1.37 g/cm^3
Structural formula:	



Cloquintocet-mexyl

Common name:	cloquintocet-mexyl
Chemical name:	2-heptyl-5-chloro-8-quinolinoxy-acetate
Product name:	TOPIK SELECTIVE HERBICIDE
CAS Registry Number	99607-70-2
Molecular formula:	$C_{18}H_{22}ClNO_3$
Molecular weight:	335.83
Appearance (colour):	light brown
Odour:	odourless
Physical state:	powder
Relative density:	approx. 1.26 g/cm^3
Structural formula:	



4. AGRICULTURAL ASSESSMENT

Justification for Use

Effective weed control in the target crop (wheat) is essential for economic production. The introduction of TOPIK SELECTIVE HERBICIDE will complement the weed control spectrum achieved by existing herbicides.

Proposed Use Pattern

TOPIK will be applied to wheat once per season by aircraft or ground based equipment. TOPIK is to be applied only when weeds are growing. Mixing of TOPIK is with water and a suitable adjuvant. The maximum application rate is 170 mL/ha.

Evaluation of Efficacy

The applicant, CIBA-GEIGY Australia Limited, has provided considerable and comprehensive efficacy and phytotoxicity data to support the claims of TOPIK. Over 100 trials have been conducted in Australia. TOPIK was trialed at three levels of formulation: 15g, 21g, and 39g active ingredient/hectare. All formulations provided equivalent weed control when applied at equivalent rates.

Trial design (control plots, number of treatments, replicates) was satisfactory while the trials - which were conducted in several States (and covered a wide variety of soil types, climates and conditions) have been adequately recorded and analysed. Trial results were validated by qualified personnel from recognised companies and authorities.

Phytotoxicity

There were no significant phytotoxic effects on the target crop wheat. Trial results are:

- WA: wheat varieties showed good tolerance to TOPIK even when applied at rates well above those required for weed control;
- VIC/SA: all the wheat cultivars tested in VIC and SA showed good tolerance to TOPIK at rates well above those required for weed control;
- NSW: all the wheat varieties tested in NSW showed good tolerance to TOPIK at rates above those required for weed control.

Conclusion

The results of the above trials showed that TOPIK is effective.

5. ENVIRONMENTAL ASSESSMENT

TOPIK will be applied to wheat once per season as a medium to coarse spray using aircraft or ground based equipment. Environmental exposure will principally involve the soil, as water solubility and vapour pressure are low. The following environmental tests were carried out on the active constituents clodinafop-propargyl and cloquintocet-mexyl.

CLODINAFOF-PROPARGYL

Environmental Fate

Hydrolysis

Clodinafop-propargyl proved hydrolytically unstable under neutral and especially under alkaline conditions. Half-lives at 20°C ranged from 184 d at pH 5 through 64 h at pH 7 to 2.2 h at pH 9. Clodinafop acid was the only product observed.

Photolysis

Clodinafop-propargyl degraded rapidly in solution when irradiated with a xenon lamp. However, photolysis on soil, a more likely degradation pathway on exposure grounds, proved relatively slow.

Metabolism in Soils and Aquatic Systems

The main pathway for degradation of clodinafop-propargyl in the environment will be microbial metabolism in soils. This was found to proceed rapidly (half-lives less than a day) in a range of soils. Two transient metabolites, clodinafop acid and 5-chloro-3-fluoro-2-hydroxypyridine, were formed soon after application to the soils. Both degraded further to bound residues and carbon dioxide.

Hydrolysis to the acid also occurred rapidly (half-life less than a day) in a model aquatic system. Further breakdown of the acid led via the pyridine metabolite to bound residues and carbon dioxide, with only small amounts of other metabolites.

Mobility in Soil

Soil organic carbon partition coefficients obtained from adsorption/desorption studies on five soils were generally indicative of strong adsorption, the exception being one loamy sand where adsorption was moderate.

The low soil mobility of clodinafop-propargyl was confirmed by leaching tests on packed columns of various soils. Unchanged ester was only found at trace levels in the surface layer of some soils. However, significant amounts of the acid metabolite leached through some of the soils, indicating that the free acid form of the new herbicide should be considered mobile in soil.

Mobility was greatly reduced when clodinafop-propargyl was aged on soil for 28 d before commencing leaching tests. Less than 5% of applied was recovered as degradation products from the leachates.

Field Dissipation

Reports of field studies confirmed the rapid degradation and low leaching expected from laboratory results.

Accumulation and Bioaccumulation

Accumulation in soils is not expected in view of the rapid dissipation. This was confirmed in a four year field study, in which residues remained below the lower practical limits of analysis (0.05 mg.kg⁻¹).

The bioaccumulation potential is low because of the rapid degradation of the ester and hydrophilicity of the acid metabolite.

Environmental Effects

Birds

Acute oral and dietary tests indicated that clodinafop-propargyl is slightly to practically non-toxic to bobwhite quail and practically non-toxic to mallards. No clinical or behavioural abnormalities were observed.

Aquatic organisms

Test results for clodinafop-propargyl indicate high acute and chronic toxicity to fish. The most sensitive species was the bluegill sunfish (96 h LC50 0.21 ppm). Acute toxicity to water fleas is slight, increasing to high under conditions of chronic exposure. The EC50 for reproductive effects in water fleas was 0.039 ppm. Toxicity to algae and duckweed is slight to moderate.

Further testing on the primary metabolite indicated that clodinafop acid is practically nontoxic to fish and slightly toxic to algae and duckweed.

Non-target invertebrates

Clodinafop-propargyl proved practically nontoxic to bees exposed by contact or oral routes. Similarly, no significant toxic effects were observed in earthworms exposed for 14 d in an artificial soil test.

Non-target plants

No specific data are available. Any phytotoxic potential should be restricted to certain grass species by analogy with other herbicides from this class.

Environmental Hazard

No wildlife hazard is anticipated from the proposed use as clodinafop-propargyl has low to negligible toxicity to terrestrial organisms.

A worst case scenario of direct application to 15 cm of standing water at the highest proposed rate would result in a concentration of 34 ppb, about an order of magnitude below

96 h LC50s for fish. Thus a narrow margin of safety exists in this hypothetical situation of direct overspray of a very shallow pond.

The label contains comprehensive spraying instructions and advises against application if rain is expected within 2 h, thus minimising the risk of aquatic contamination through drift or runoff. Given the limited aquatic persistence and lack of sensitivity of fish to the rapidly formed acid metabolite, it may be assumed that aquatic hazard from the proposed use on wheat is low.

The above concentration approximates the nominal end-point in the *Daphnia* reproduction test. However, chronic exposure of aquatic organisms is not anticipated because of the infrequency of application and ease of hydrolysis.

The predicted environmental concentration is at least two orders of magnitude below end-points for algae and duckweed exposed to clodinafop-propargyl or its acid metabolite. Hazard to aquatic flora is low.

Hazard to native vegetation appears low as broad leafed plants are tolerant of this class of herbicide, and significant exposure of non-target vegetation would not be expected to arise in the context of the proposed broadacre use on wheat.

CLOQUINTOCET-MEXYL

Hydrolysis

Cloquintocet-mexyl proved hydrolytically unstable under alkaline conditions. Half-lives at 20°C ranged from 4.4 years at pH 5 through 134 days at pH 7 to 6.6 days at pH 9. Cloquintocet acid was the only product observed.

Photolysis

Cloquintocet-mexyl degraded rapidly in solution when irradiated with a xenon lamp. However, photolysis on soil, a more likely degradation pathway on exposure grounds, proved relatively slow.

Metabolism in Soils and Aquatic Systems

The main pathway for degradation of cloquintocet-mexyl in the environment will be microbial metabolism in soils. This was found to proceed rapidly (half-lives less than three days) in a range of soils. A single transient metabolite, cloquintocet acid, formed soon after application to the soils, degrading further to bound residues and carbon dioxide.

Hydrolysis to the acid also occurred rapidly (half-life less than a day) in a model aquatic system. Further breakdown of the acid led to sediment bound residues and carbon dioxide.

Mobility in Soil

Soil organic carbon partition coefficients obtained from adsorption/desorption studies on five soils were indicative of strong adsorption.

The low soil mobility of cloquintocet-mexyl was confirmed by leaching tests on packed columns of various soils. Unchanged ester was only found at trace levels in the surface layers. Significant amounts of the acid metabolite were also formed, but none was detected below 6 cm, indicating that both ester and free acid form of the new safener should be considered immobile in soil.

Field Dissipation.

Reports of field studies confirmed the rapid degradation expected from laboratory results.

Accumulation and Bioaccumulation.

Accumulation in soils is not expected in view of the rapid dissipation and single application per season.

Flow-through tests on bluegill sunfish indicate a moderate bioaccumulation factor, but, most of the accumulated residue was cloquintocet acid, assumed to have formed from the ester almost immediately after absorption. Residues were rapidly eliminated when the fish were returned to clean water, consistent with the hydrophilicity of the acid metabolite.

Environmental Effects

Birds

Acute oral and dietary tests indicated that cloquintocet-mexyl is practically non-toxic to bobwhite quail and mallards. No clinical or behavioural abnormalities were observed.

Aquatic organisms

Test results for cloquintocet-mexyl indicate slight acute and moderate chronic toxicity to fish. The most sensitive species was the catfish (96 h LC50 14 ppm). The safener is practically nontoxic to water fleas under conditions of acute exposure, but very highly toxic (21 d EC50 2 ppb) under conditions of chronic exposure. Toxicity to algae is also high, with the 72 h EC50 for the most sensitive species being 0.53 ppm. Toxicity to duckweed appears moderate.

Further testing on the primary metabolite indicated that cloquintocet acid is practically nontoxic to fish and green algae, but moderately toxic to duckweed, blue algae and diatoms.

Non-target invertebrates

Cloquintocet-mexyl proved practically nontoxic to bees exposed by contact or oral routes. Similarly, no significant toxic effects were observed in earthworms exposed for 14 d in an artificial soil test.

Non-target plants

No data were included in the submission. The safener is intended to protect against crop phytotoxicity, and is not known to have herbicidal properties.

Environmental hazard

No wildlife hazard is anticipated from the proposed use as cloquintocet-mexyl has low to negligible toxicity to terrestrial organisms.

A worst case scenario of direct application to 15 cm of standing water at the highest proposed rate would result in a concentration of 8 ppb, more than three orders of magnitude below acute end-points for aquatic fauna. Thus a broad margin of safety exists even in this hypothetical situation of direct overspray to a very shallow pond.

The estimated concentration exceeds the EC50 from the *Daphnia* reproduction test, but chronic exposure situations will not arise given the infrequency of application and limited persistence.

The label contains comprehensive spraying instructions and advises against application if rain is expected within 2 h, thus minimising the risk of aquatic contamination through drift or runoff. Therefore, it may be assumed that aquatic hazard from the proposed use on wheat is low.

Adequate safety margins also exist for algae, as the most sensitive end-point is some 60 times higher than the concentration estimated above, and neither cloquintocet-mexyl nor its primary acid metabolite persist in the water column. Hazard to duckweed is also low.

Hazard to native vegetation appears low as cloquintocet-mexyl is not known to have any phytotoxic properties, and significant exposure of nontarget vegetation would not be expected to arise in the context of the proposed broadacre use on wheat.

6. PUBLIC HEALTH AND SAFETY ASSESSMENT

CLODINAFOF-PROPARGYL

Evaluation of Toxicology

The toxicological database for clodinafop-propargyl, which consists primarily of toxicity tests conducted using animals, is quite extensive. In interpreting the data, it should be noted that toxicity tests generally use doses which are high compared to likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified. Toxicity tests should also indicate dose levels at which the specific toxic effects are unlikely to occur. Such dose levels as the No-Observable-Effect-Level (NOEL) are used to develop acceptable limits for dietary or other intakes at which no adverse effects in humans would be expected.

Toxicokinetics and Metabolism

After single oral administration to rats, clodinafop-propargyl was well absorbed, hydrolysed to the propionic acid form, and excreted in urine and to a lesser extent in faeces, with some accumulation in fat tissue. Approximately 34% of a dermal dose was absorbed through the skin of rats.

Acute Studies

Clodinafop-propargyl has low acute oral (LD50 = 1392 mg/kg bw), dermal (LD50 > 2000 mg/kg bw) and inhalation toxicity (LC50 > 2325 mg/m³) in rats, is not a skin irritant but is a slight eye irritant in rabbits and is a skin sensitizer in guinea pigs.

No studies conducted with Topik Selective Herbicide, the formulation containing 300 g/L clodinafop-propargyl and 75 g/L cloquintocet-mexyl, were available. Based on toxicological data available for the formulation components, Topik Selective Herbicide is likely to be an eye irritant and a skin sensitizer.

Repeat Dose Studies

The liver was the major target organ for toxicity in rodents in 28-day gavage and 3-month dietary studies, with increased liver weights, enlargement of liver cells, increases in liver enzyme activities, and focal liver necrosis occurring following oral exposure to clodinafop-propargyl from 10 mg/kg bw/day in rats and 15 mg/kg bw/day in mice. Dogs treated with clodinafop-propargyl in the diet for 3 months also showed moderate increases in liver weights and liver enzyme activities from 7.5 mg/kg bw/day. Most of the liver effects were reversible

after cessation of treatment. Other toxic effects included skin inflammation (only in dogs), anaemia, and atrophy of the bone marrow, spleen and thymus.

Carcinogenicity Studies

An 18-month dietary study in mice showed several signs of liver toxicity at the two highest doses, 15 and 37.5 mg/kg bw/day. At the highest dose the incidences of benign and malignant liver tumours in males, and benign and malignant liver blood vessel tumours in females, were slightly increased. With the exception of benign liver tumours in high-dose males, all tumour incidences were within the normal range in untreated mice.

A 24-month dietary study in rats showed several signs of liver toxicity at doses of 10 mg/kg bw/day and above. At only the highest dose (37.5 mg/kg bw/day), the incidences of liver tumours in males, and benign tumours of the prostate, and benign tumours of the ovary tubule were moderately increased. The incidence of liver tumours in high-dose males was within the normal range in untreated rats.

Clodinafop-propargyl has been shown to cause peroxisome proliferation in rodents, which may lead to the development of liver tumours. Although rats and mice are sensitive to this mechanism, human liver cells cultured with clodinafop-propargyl did not proliferate indicating that peroxisome proliferation effects in humans are unlikely.

Reproduction and Developmental Studies

Clodinafop-propargyl had no effects on reproduction parameters in a 2-generation rat study. Physical development of pups was slightly delayed only at the highest dose (100 mg/kg bw/day), which also produced liver and kidney toxicity in parents of both generations.

Clodinafop-propargyl did not produce birth defects in rats or mice when administered orally during organogenesis, however foetal growth was slightly slowed in rats at a dose which also resulted in maternal toxicity (40 mg/kg bw/day).

Genotoxicity

Clodinafop-propargyl was not mutagenic in bacteria or mammalian cells in vitro, did not cause unscheduled DNA synthesis in cultured rat and human cells in vitro, and showed no evidence of chromosomal damage to mammalian cells in vivo. These studies indicate that clodinafop-propargyl does not cause damage to genetic material (DNA).

Public Health Standards

Poisons Scheduling

The National Drugs and Poisons Schedules Committee (NDPSC) considered the toxicity of the product and its active ingredients and assessed the necessary controls to be implemented under States' poisons regulations to prevent the occurrence of poisoning.

The NDPSC recommended that clodinafop-propargyl be listed in Schedule 6 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). There are provisions for appropriate warning statements and first-aid directions on the product label.

No Observable Effect Level / Acceptable Daily Intake

The most sensitive species was the rat, with a NOEL of 0.37 mg/kg bw/d. In order to calculate the acceptable daily intake (ADI) for humans, a safety factor is applied to the NOEL in the most sensitive species. The magnitude of the safety factor is selected to account for uncertainties in extrapolation of animal data to humans; variation within the human population; the quality of the experimental data; and the nature of the potential hazards. Using a safety factor of 100, an ADI of 0.0037 mg/kg bw/d for clodinafop-propargyl was established.

CLOQUINTOCET-MEXYL

Evaluation of Toxicology

The toxicological database for cloquintocet-mexyl, which consists primarily of toxicity tests conducted using animals, is quite extensive. In interpreting the data, it should be noted that toxicity tests generally use doses which are high compared to likely human exposures. The use of high doses increases the likelihood that potentially significant toxic effects will be identified. Toxicity tests should also indicate dose levels at which the specific toxic effects are unlikely to occur. Such dose levels as the No-Observable-Effect-Level (NOEL) are used to develop acceptable limits for dietary or other intakes at which no adverse effects in humans would be expected.

Toxicokinetics and Metabolism

After single oral administration to rats, 37-53% of the total dose was absorbed, and 60% of the total dose was excreted in faeces and 35-39% in urine, within 24 hours.

Acute Studies

Cloquintocet-mexyl has low acute oral (LD50 > 5000 mg/kg bw), dermal (LD50 > 2000 mg/kg bw) and inhalation toxicity (LC50 > 935 mg/m³) in rats, and is not a skin irritant, but is a slight eye irritant in rabbits, and a skin sensitizer in guinea pigs.

No studies conducted with Topik Selective Herbicide, the formulation containing 300 g/L clodinafop-propargyl and 75 g/L cloquintocet-mexyl, were available. Based on toxicological data available for the formulation components, Topik Selective Herbicide is likely to be an eye irritant and a skin sensitizer.

Short-Term Studies

Effects in dietary studies of up to 3 months duration included increased white blood cells, anaemia, elevated liver enzyme activities and increased liver and kidney weights in rats from 10 mg/kg bw/day; and anaemia, increased red blood cell production in the bone marrow and spleen, atrophy of the thymus, and decreased testes and prostate weights in dogs from 30 mg/kg bw/day. A dermal study in rats showed no effects at doses up to 1000 mg/kg bw/day.

Long-Term Studies

Long-term studies showed reduced bodyweights, increased water consumption, and chronic inflammation of the lining of the urinary bladder in mice at 520 mg/kg bw/day, increased cells in the thyroid follicular epithelium in female rats at 36 mg/kg bw/day, and reduced bodyweights, reduced bone marrow cells, increased liver enzyme activities and increased liver weights in dogs at 37 mg/kg bw/day. There was no evidence of tumourigenicity in rats or mice.

Reproduction and Developmental Studies

Reproduction parameters were not adversely affected in a 2-generation rat study. Offspring bodyweights were lower at the high dose only (1000 mg/kg bw/day). There was no evidence of birth defects in studies in rats and rabbits. Slight delays in foetal ossification were associated with maternal toxicity in both species.

Genotoxicity

Cloquintocet-mexyl was not mutagenic in bacteria and mammalian cells in vitro, and was negative in an in vivo micronucleus test, indicating that it does not damage genetic material (DNA).

Public Health Standards

Poisons Scheduling

The National Drugs and Poisons Schedule Committee (NDPSC) considered the toxicity of the product and its active ingredients and assessed the necessary controls to be implemented under States' poisons regulations to prevent the occurrence of poisoning.

The NDPSC recommended that cloquintocet-mexyl be listed in Schedule 5 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). There are provisions for appropriate warning statements and first-aid directions on the label.

No Observable Effect Level / Acceptable Daily Intake

The most sensitive species was the rat, with a NOEL of 4 mg/kg bw/d. In order to calculate the acceptable daily intake (ADI) for humans, a safety factor is applied to the NOEL in the most sensitive species. The magnitude of the safety factor is selected to account for uncertainties in extrapolation of animal data to humans; variation within the human population; the quality of the experimental data; and the nature of the potential hazards. Using a safety factor of 100, an ADI of 0.04 mg/kg bw/d for cloquintocet-mexyl was established.

Potential for Chemical Residues in Food

Results of twenty overseas residue trials, and of four Australian trials, showed that the proposed Australian use pattern of TOPIK should not give rise to measurable residues. Animal transfer studies were not required because the metabolism and residue results show that it is unlikely that measurable residues would occur in animals fed with treated produce.

Details of these trials follow:

Metabolism Data

CLODINAFOP-PROPARGYL

Results from two studies on spring wheat treated with carbon 14 labelled propargyl ester at a rate of 2.45 times the proposed maximum Australian use rate showed that residues of clodinafop-propargyl and its acid hydrolysis product were not detected in harvested wheat. The absence of parent throughout the wheat's growth was also demonstrated together with an increase in the levels of non-extractable radioactivity as the wheat grew and matured.

Two rotational crop studies measured the amount of uptake of radiolabel in crops planted in the ground where spring wheat had been treated with carbon 14 labelled propargyl ester at a rate of 2.45 times the proposed maximum Australian use rate. The studies demonstrated the absence of transfer of radioactivity to the rotational crops (lettuce, winter wheat, corn and sugar beet) with all levels of radiolabel found being less than or equal to 0.001 ppm. Because of the very low level of radiolabel found, the studies made no attempt to characterise the labelled material.

Results of metabolism studies on a lactating goat and on laying hens were also provided. Radiolabelled clodinafop-propargyl was fed to a lactating goat at a rate of about 5.9 ppm in the feed for 10 days and to laying hens for 14 days at about 5 ppm in the feed.

In the goat study, faeces, urine and milk were collected and muscle, fat, and offal samples taken from the killed animal. The study did not investigate the nature of the radiolabelled material found. The majority of the administered dose was recovered in the faeces and cage wash. Milk and tissues were shown to contain only a minor amount of radiolabelled material. The main source of elimination was via the urine. Levels in milk reached a plateau by 72 hours at 0.16 to 0.17% of the daily dose. Levels of residues in the tissues (as equivalents of clodinafop-propargyl) were: milk 0.014 ppm, muscle tissue ≤ 0.001 ppm, fat 0.002-0.004 ppm, liver 0.011 ppm and kidney 0.077 ppm. These values are taken as indicative metabolism/excretion occurring in the kidneys and liver and a lack of accumulation in tissues and fat.

In the laying hen study, faeces, eggs and cage wash were collected and blood, muscle, skin, fat, kidney and liver samples taken from the slaughtered birds. The majority of the dose was excreted with only small amount of radiolabel found in tissues and eggs. The amount of radiolabel reached a plateau in eggs by 168 hours at 0.1-0.2% of the daily dose (< 0.01 ppm equivalents of clodinafop-propargyl). The highest levels of radioactivity, as equivalents of clodinafop-propargyl, were in the kidney (3.16 ppm) and liver (0.14 ppm). In fat and lean meat, residue levels were low (< 0.05 ppm). These results are consistent with excretion via the kidneys and lack of uptake into fat. Clodinafop-propargyl and its acid hydrolysis product were not found in the kidney residue.

These animal metabolism studies indicated that clodinafop-propargyl was metabolised by the lactating goat and laying hens and accumulation of residues in tissues or fat was not demonstrated.

A rat study was reported in which female rats were given a single dose of radiolabelled clodinafop-propargyl and the rate of absorption and excretion measured. The nature of metabolites formed was not investigated. Urine was the main source of elimination (65 to 97% of the administered dose). Faeces contained 5 to 19% of the dose. Elimination was considered to be rapid and essentially complete. Peak urine levels were seen between 48 and 72 hours. By 96 hours the levels had reached levels equal to those found 4 hours after dosing and were continuing to decline. Maximum blood and plasma residue levels were reached by 8 hours. By 50 hours the plasma and blood radioactivity levels were approaching zero residue levels.

The plant and animal metabolism studies showed a ready loss of clodinafop-propargyl and its primary acid metabolite. The studies also indicated that the presence of these residues in wheat and wheat products and in animals fed treated wheat or wheat products was unlikely to arise from the proposed use pattern.

CLOQUINTOCET-MEXYL

A metabolism study in which spring wheat was treated with radiolabelled cloquintocet-mexyl at a rate of approximately 3.5 times the proposed Australian maximum rate showed that residues of cloquintocet-mexyl on the leaves had disappeared by 21 days after treatment. Grains, husks and straw were shown to have less than 0.005 ppm of cloquintocet-mexyl present. In a stem injection experiment conducted with the study, absence of parent in grains and husks and the presence of 5-chloro-8-quinolinoxyacetic acid, the acid hydrolysis product

of cloquintocet-mexyl, were demonstrated.

A rotational crop study was reported in which lettuce, winter wheat, corn and sugar beet were grown in soil in which spring wheat had been treated with carbon 14 labelled cloquintocet-mexyl (at approximately 4 times the proposed maximum Australian rate). Negligible radioactivity was found in the crops during growth and at maturity, indicating that transfer from the soil did not occur. Because of the low levels of radiolabel taken up by the crops, the nature of the radiolabel was not investigated.

Results of a lactating goat and laying hen metabolism trials in which these animals were fed carbon 14 labelled cloquintocet-mexyl at levels of 5 ppm in the feed for 10 and 14 days respectively were also presented. 5-Chloro-8-quinolinoxyacetic acid was the only metabolite identified by the studies.

The goat study showed that the main source of elimination was via the urine and faeces. Milk and selected tissues contained only a minor fraction of the radiolabel. Milk levels reached a plateau after 72 hours at about 0.01 ppm of radiolabelled material. Residues of radiolabel material in tissues, expressed as equivalents of cloquintocet-mexyl, were low - kidney had the highest level, 0.024 ppm. Fat levels were <0.001 ppm.

Results from the laying hen study showed the excreta was the main source of elimination of the radiolabelled material. Tissues and eggs had very little radiolabel present. Kidneys had the highest level of residues (about 0.04 mg/kg of cloquintocet-mexyl equivalents).

These studies indicated that cloquintocet-mexyl was metabolised by the lactating goat and laying hens. Accumulation of residues in tissues or fat was not demonstrated. The studies also indicated the need to include 5-chloro-8-quinolinoxyacetic acid in the residue definition.

The plant and animal metabolism studies showed a ready loss of cloquintocet-mexyl and its primary acid metabolite. The studies also indicated the presence of these residues in wheat and wheat products and in animals fed treated wheat or wheat products was unlikely to arise from the proposed use pattern.

Analytical Methodology

Analytical methods for the determination of clodinafop-propargyl and cloquintocet-mexyl and their primary acid metabolites in wheat, wheat plants and fodder and forage were presented.

The esters were determined by extraction with acetonitrile and the extract cleaned up by column chromatography followed by dilution with a reducing sulphite buffer solution and extraction into dichloromethane. The solvent was evaporated and the residue dissolved in dichloromethane/hexane and chromatographed successively on quaternary methylamine and carboxyl methyl cartridges. The esters were determined by HPLC on a reverse phase C18 column with ultraviolet detection at 233 nm. The limit of determination was the lowest concentration at which satisfactory ($\geq 70\%$) recovery was reported. The data presented indicated this was 0.05 mg/kg.

The acids were determined by maceration with acetone buffer, column chromatography, addition of sodium chloride solution and partitioning into dichloromethane/ether/acetone. The solvent was evaporated and the residue separated into the acid fractions by HPLC on a C18 column. Determination was at 226 nm for the clodinafop-propargyl derived acid and 243 nm for the 5-chloro-8-quinolinoxy- acetic acid. The limit of determination was the lowest concentration at which satisfactory ($\geq 70\%$) recovery was reported. The data presented indicated this was 0.1 mg/kg.

Methods for the determination of residues in muscle, kidney, liver, fat and milk were proposed based on the above methods. These methods had not been validated for such uses. It has been made a condition of clearance that data to validate these methods be presented to the National Registration Authority within two years of clearance.

Residue Definition

The metabolism and residue data presented indicated that the primary acid metabolites as well as the starting esters should be included in the residue definitions. The residue definitions decided on are:

Clodinafop-propargyl	Clodinafop-propargyl
Clodinafop acid	(R)-2-[4-(5-chloro-3-fluoro-2-pyridyloxy)-phenoxy]-propionic acid
Cloquintocet-mexyl	Cloquintocet-mexyl
Cloquintocet acid	5-chloro-8-quinolinoxyacetic acid

Residue Data

Results of four Australian residue trials conducted on wheat were presented. Three trials were conducted in New South Wales and one in Queensland. Application rates used were 97% and 190% of the maximum label rate. A single application was applied according to the label directions. In two trials a crop spraying mineral oil was mixed with the product before application. A rapid decline in residue levels of both actives and their acid hydrolysis products was seen. Fourteen days after treatment, residues of the active constituents and their acid hydrolysis products were not found in the trials conducted at the higher application rate. At the lower application rate only one sample contained a detectable residue (clodinafop-propargyl, 0.04 mg/kg). No residues were detected in wheat treated at the higher application rate. The presence of mineral oil did not affect residue levels.

Results of twenty overseas trials were also supplied in support of the application. These trials were conducted in South Africa, Canada, England, Argentina, Italy, Switzerland and France. The use patterns in these trials were comparable to that proposed for Australia with the amount of TOPIK applied equivalent to or greater than the amount proposed for use in Australia. The results of the overseas trials supported the Australian trials findings and showed there was an absence of measurable residues 4 weeks after treatment. The overseas results also showed the absence of measurable residues in wheat grain, straw and husks.

These data and the consistency of results found in all the trials submitted supported the applicant's proposal that MRLs in wheat and wheat fodder and forage were below the limits of determination of the analytical methods used in the trials for clodinafop-propargyl and cloquintocet-mexyl and for clodinafop acid and cloquintocet acid (the primary acid metabolites). The results also indicate that the proposed Australian use pattern should not give rise to measurable residues. The wheat fodder and forage MRLs proposed on the basis of this review have been expressed on a "wet weight basis" because the results presented were on the wheat and plant material as received and were not reported on a "dry weight" basis. The absence of moisture contents made it impractical to express the MRLs on a "dry weight" basis.

Animal commodity MRLs were requested by the applicant and supported by the argument that as residues were not measurable in fodder, forage or grain, transfer to animals eating treated produce would not be expected to occur. The metabolism data supported the applicant's argument, as active breakdown and excretion of the actives and their metabolites was demonstrated together with indications that accumulation of residues did not take place. For these reasons and because the anticipated dietary intake from the use of the chemicals was acceptable, the argument for animal commodity MRLs was accepted.

Animal transfer studies were not required because the metabolism and residue results had shown that it was unlikely that measurable residues would occur in animals fed treated produce. This decision was supported by daily intake calculations of residues indicating the maximum intakes of clodinafop-propargyl and cloquintocet-mexyl would be less than 6 and 0.6% respectively of their Acceptable Daily Intakes. This decision was consistent with the FAO/WHO Joint Meeting on Pesticide Residues' (JMPR) guideline that where residue levels are expected to be <0.1 mg/kg, animal feeding studies are not required if dietary intake and metabolism studies have been considered and found satisfactory (Pesticide Residues in Food - 1993, FAO Plant Production and Protection Paper 122, pages 7 and 8).

Withholding Periods and MRLs

The residue data and proposed use pattern indicated that the following withholding period statements are appropriate:

WITHHOLDING PERIOD:

For harvested grain - NOT REQUIRED

For animal grazing/feeding - DO NOT GRAZE OR CUT FOR STOCK FOOD FOR 4 WEEKS AFTER APPLICATION

The residue and metabolism data showed that when the product is used according to the proposed label, including the withholding periods, the proposed MRLs should not be exceeded.

The following consequential amendments have been recommended to the MRL Standard:

TABLE 1

Compound	Food	MRL (mg/kg)
Delete:		
Cloquintocet		
GC 0654	Wheat	T*0.02
Piroxofop		
CG 0654	Wheat	T*0.02
Add:		
Clodinafop-propargyl		
MO 0105	Edible offal, mammalian	*0.05
PE 0112	Eggs	*0.05
MM 0095	Meat (mammalian)	*0.05
ML 0106	Milks	*0.05
PO 0111	Poultry, edible offal	*0.05
PM 0110	Poultry meat	*0.05
GC 0654	Wheat	*0.05
Clodinafop acid		
MO 0105	Edible offal, mammalian	*0.1
PE 0112	Eggs	*0.1
MM 0095	Meat (mammalian)	*0.1
ML 0106	Milks	*0.1
PO 0111	Poultry, edible offal	*0.1
PM 0110	Poultry meat	*0.1
GC 0654	Wheat	*0.1
Cloquintocet-mexyl		
MO 0105	Edible offal, mammalian	*0.05
PE 0112	Eggs	*0.05
MM 0095	Meat (mammalian)	*0.05
ML 0106	Milks	*0.05
PO 0111	Poultry, edible offal	*0.05
PM 0110	Poultry meat	*0.05
GC 0654	Wheat	*0.05
Cloquintocet acid		
MO 0105	Edible offal, mammalian	*0.1
PE 0112	Eggs	*0.1
MM 0095	Meat (mammalian)	*0.1
ML 0106	Milks	*0.1
PO 0111	Poultry, edible offal	*0.1
PM 0110	Poultry meat	*0.1
GC 0654	Wheat	*0.1

NOTE 1 TO TABLE 1: "Cloquintocet" and "Piroxofop" were names originally applied to cloquintocet-mexyl and clodinafop-propargyl.

NOTE 2 TO TABLE 1: "*" indicates the MRLs have been set at or about the limit of determination.

Establish the following Table 3 and Table 4 entries:

TABLE 3

Compound	Residue
Delete: Cloquintocet Piroxofop	Cloquintocet Piroxofop
Add: Clodinafop-propargyl Clodinafop acid	Clodinafop-propargyl (R)-2-[4-(5-chloro-3-fluoro-2-pyridyloxy)-phenoxy]- propionic acid
Cloquintocet-mexyl Cloquintocet acid	Cloquintocet-mexyl 5-Chloro-8-quinolinoxyacetic acid

TABLE 4

Compound	Animal Feed Commodity	MRL (mg/kg)
Clodinafop-propargyl	Wheat straw and fodder (wet weight basis)	*0.1
Clodinafop acid	Wheat straw and fodder (wet weight basis)	*0.1
Cloquintocet-mexyl	Wheat straw and fodder (wet weight basis)	*0.1
Cloquintocet acid	Wheat straw and fodder (wet weight basis)	*0.1

NOTE 1 TO TABLE 4: "*" indicates the MRLs have been set at or about the limit of determination.

NOTE 2 TO TABLE 4: The MRLs are expressed on a "wet weight" or "as is" basis and not corrected for moisture content.

Codex Alimentarius Commission

As at April 1994 there were no Codex MRLs for the compounds under consideration.

Fat Solubility

The evaluation indicated that clodinafop-propargyl and cloquintocet-mexyl could be expected to exhibit fat-solubility. These esters however very rapidly convert to acids which have little potential for bioaccumulation.

Implications for Trade

Residue data from Australia and overseas, using use patterns equivalent to that proposed for Australia, showed residues of the actives and their primary acid products rapidly decreased to the point of not being measurable. At the withholding period proposed for treated wheat plants, measurable residues were not found. Similarly, residues were not measurable in wheat or wheat fodder and forage. Also, the data and argument supplied supported the applicant's proposals that residues in animal commodities would not be measurable.

TOPIK is therefore deemed to present no hazard to Australia's export trade.

7. OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Clodinafop-propargyl and cloquintocet-mexyl are hazardous substances according to the National Occupational Health and Safety Commission (NOHSC) Approved Criteria for Classifying Hazardous Substances.

The product, TOPIK, is also a hazardous substance according to NOHSC criteria. It appears as a dark amber liquid with an ester-like odour.

TOPIK will be formulated in Australia from imported clodinafop-propargyl and cloquintocet-mexyl. Both active constituents exist as odourless powders.

Clodinafop-propargyl, cloquintocet-mexyl and TOPIK are not classified as dangerous goods under the Australian Code for the Transport of Dangerous Goods by Road and Rail.

Formulation, Packaging, Transport and Sale

Australian workers involved in formulation, testing, and packing of the active ingredients or product should be protected by a fully enclosed formulation process, air extraction, safe work practices and training commensurate with risks identified in the workplace assessment. These workers should wear overalls, approved safety boots, fully enclosed goggles and PVC or nitrile rubber gloves.

Australian workers involved in transport, storage and retailing could only become contaminated with the active ingredients or product if the packaging were breached.

Advice on the safe handling of clodinafop-propargyl and cloquintocet-mexyl during routine use, transport and storage is provided on clodinafop-propargyl and cloquintocet-mexyl labels and in the material safety data sheet (MSDS) for each active constituent. The TOPIK MSDS contains information on how to deal with storage, transport and spillage.

End Use

TOPIK may be applied by ground or aerial spraying, for weed control in wheat. The concentration of product in the spray ranges from 0.045% to 0.85%.

End users may become contaminated with TOPIK when preparing the working strength solution, loading spray tanks and applying the spray. Workers will also need to clean up spills and maintain and clean spray equipment.

Use of TOPIK is seasonal, but contract workers may handle it frequently over the spraying season.

TOPIK is expected to be of low acute toxicity but may be a skin and eye irritant and a skin sensitiser. It is important for users to protect the skin and eyes when pouring out the concentrated product. Safety directions on the label caution workers to avoid skin and eye contact with the product and avoid inhaling spray mist. They include the use of cotton overalls and washable hat, elbow-length PVC gloves and a face shield or goggles for workers mixing and loading the product.

Contamination with spray solution is not expected to result in substantial contamination or health effects in end users. Specific protective clothing is not considered necessary for workers using the spray. All workers should adopt good occupational hygiene practices.

End users should follow the directions on the TOPIK label and refer to the MSDS for additional information.

Entry Into Treated Areas

Entry into treated fields does not pose any occupational health and safety concern and Worksafe Australia does not recommend a restricted-entry statement at this time.

Recommendations For Safe Use - All Workers

Workers involved in formulating and packaging the product should be protected by engineering controls such as an enclosed formulation process and air extraction, safe work practices and training. They should also wear long sleeved overalls (AS 3765-1990 Clothing for protection against hazardous chemicals), approved safety boots (AS 2210 Occupational protective footwear), fully enclosed goggles (AS 1337-1984 Eye protectors for industrial applications) and PVC or nitrile rubber gloves (AS 2161-1978 Industrial safety gloves and mittens).

End users should adhere to the directions on the TOPIK label. They need to wear cotton overalls and washable hat, elbow-length PVC gloves and face shield or goggles when mixing and loading the product.

On the basis of this risk assessment, Worksafe Australia does not consider that occupational health and safety regulatory standards, such as Health Surveillance or assigning Exposure Standards, are necessary for clodinafop-propargyl and cloquintocet-mexyl.

Conclusion

Clodinafop-propargyl, cloquintocet-mexyl and TOPIK can be used safely if handled in accordance with the control measures described above. Additional information is available on the TOPIK label and in the respective MSDS.

TOPIK Selective Herbicide - International Registration Update

Countries where products containing clodinafop-propargyl plus cloquintocet-mexyl are registered:

Country	Formulation Type	Registration Number	Crops
Argentina	80 EC	-	Wheat
Belgium	240 EC	8460/B	Wheat, rye, triticale
Chile	240 EC	3221	Wheat
Czech Republic	80 EC	3821	Winter wheat
France	100EC	9100645	Winter wheat
Greece	80 EC	7446	Wheat
Hungary	80 EC	15334/1994	Winter wheat
Israel	100 EC	1222	Wheat
Netherlands	-	-	Wheat
Paraguay	240 EC	64	Wheat
Portugal	80 EC	2580	Wheat
Romania	80 EC	1362	Wheat
Russia	80 EC	770323	Wheat
Saudi Arabia	240 EC	1891-60-119	Wheat
South Africa	240 EC	L 4250	Wheat
	8 GL	L 4677	Wheat
	80 EC	L 4777	Wheat
Switzerland	240 EC	W-4572	Rye, Winter wheat, triticale
Tunisia	100 EC	5/92	Cereals
Turkey	240 EC	2754	Wheat

POISON

NOT TO BE TAKEN

READ SAFETY DIRECTIONS BEFORE OPENING

TOPIK

SELECTIVE HERBICIDE

Active Constituents: 300 g/L CLODINAFOF-PROPARGYL
75 g/L CLOQUINTOCET-MEXYL

GROUP A HERBICIDE



**Controls Wild Oats, Paradoxa Grass
(Annual Phalaris) and
Annual Ryegrass in Wheat**

Highly active on Wild Oats and can be mixed with many broadleaf herbicides

IMPORTANT: READ THE ATTACHED LEAFLET BEFORE USE

1 LITRE

Ciba-Geigy Australia Limited
140-150 Bungaree Road, Pendle Hill, N.S.W. 2145
UFI No. free N1-0HVSW 433659

SAFETY DIRECTIONS

Will irritate the eyes and skin. Repeated exposure may cause allergic disorders. Harmful if swallowed. Avoid contact with eyes and skin. When opening the container and preparing spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and a washable hat, elbow-length PVC gloves and face shield or goggles. If product gets on skin, immediately wash area with soap and water. If product gets in eyes, wash it out immediately with water. After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water. After each day's use, wash gloves, face shield or goggles and contaminated clothing.

FIRST AID

If poisoning occurs contact a doctor or Poisons Information Centre. If swallowed, and if more than 15 minutes from a hospital, induce vomiting, preferably using Ipecac Syrup (APF).

MATERIAL SAFETY DATA SHEET

If additional hazard information is required refer to the Material Safety Data Sheet. For a copy phone 1800 02 5931.

Batch No.	
Date of Manufacture	

Topik[®]

Selective Herbicide

Active Constituents:
300 g/L CLODINAFOF-PROPARGYL
75 g/L CLOQUINTOCET-MEXYL

Complete Directions for Use Inside
- Read before using

L1 433608

ciba

Ciba-Geigy Australia Limited,
140-150 Bungaree Road, Pendle Hill, NSW 2145.

® Registered Trade Mark of Ciba-Geigy Limited, Basle, Switzerland.
• Registered Trade Mark

DIRECTIONS FOR USE:

Restraints:

DO NOT apply if rainfall is expected within 2 hours.

DO NOT apply to weeds or crops which are under stress due to, for example, very dry, very wet, frosty or diseased conditions, nutrient deficiency or high insect pressure.

Crop	Weeds Controlled	States	Rate per hectare	Critical Comments
Wheat	Wild Oats	Southern NSW, Vic, SA, WA only	50 mL to 70 mL + 1 L of DC Trate* oil per 100 L of water	Use the lower rates when Wild Oats are actively growing and are in the 2 leaf to early tillering stage (Zadoks 12-21). Use the highest rate when growing conditions are not ideal or Wild Oats are in the early to mid tillering stage (Zadoks 21-25). DO NOT apply under poor growing conditions to weeds under stress. Where low water volumes are used, DO NOT use less than 500 mL of oil per hectare. Mixtures: (see compatibility section) Apply in mixtures for broadleaf weed control ONLY when weeds are actively growing. Use 100 mL of a 100% non-ionic surfactant per 100 L of water instead of DC Trate* oil when mixing with Tigrex* or Jaguar*. Use the highest rate of TOPIK when mixing with the broadleaf weed herbicides listed as causing some reduction in grass weed control.
		Northern NSW, Qld only	70 mL to 100 mL + 1 L of DC Trate* oil per 100 L of water	
	Paradoxa Grass (<i>Phalaris paradoxa</i>)	Qld, NSW, Vic, SA only	130 mL + 1 L of DC Trate* oil per 100 L of water.	
	Annual Ryegrass	NSW, Vic, SA, WA only	130 mL to 170 mL + 1 L of DC Trate* oil per 100 L of water.	Use the lower rates when weeds are actively growing and are in the 2 to 4 leaf stage (Zadoks 12-14). Use the highest rate when growing conditions are not ideal or weeds are in the early tillering stage (Zadoks 21-25). DO NOT apply under poor growing conditions to weeds under stress. Where low water volumes are used, DO NOT use less than 500 mL of oil per hectare.

NOT TO BE USED FOR ANY PURPOSE, OR IN ANY MANNER, CONTRARY TO THIS LABEL UNLESS AUTHORISED UNDER APPROPRIATE LEGISLATION.

WITHOLDING PERIODS: For harvested grain - NOT REQUIRED.

For animal grazing/feeding - DO NOT GRAZE OR CUT FOR STOCK FOOD FOR 4 WEEKS AFTER APPLICATION.

GENERAL INSTRUCTIONS:

TOPIK Selective Herbicide should be applied only when weeds are actively growing.

MIXING:

Fill the spray tank to one quarter full. Then add TOPIK while adding water to make up the final spray volume. Pour TOPIK into the stream of incoming water. Good agitation at the time TOPIK is added to the tank will ensure good mixing. Add the required amount of DC Trate* mineral oil just before the tank is full of water and with the agitators in motion.

APPLICATION:

Ground application: Boom spray with flat fan nozzles. Ensure good spray coverage is obtained. Apply using 50 - 110 L water per hectare.

Aircraft application: For best results use 20 - 30 L water per hectare and spray at 2m to 3m above the crop. Ideal droplet size is 250 - 350 microns VMD. For rotary atomizers (micronairs) this can be achieved using blade angles of 55° - 65°. Where booms and nozzles are attached, flat fan nozzles with a spray angle of 65° - 90° should be used.

Avoid applying TOPIK if wind speeds are greater than 5 m/s. If spraying in calm conditions use larger droplets and reduce flying height.

COMPATIBILITY:

GRASS HERBICIDES: TOPIK is compatible with Hoegrass* and Nugrass*.

BROADLEAF HERBICIDES: Some broadleaf weed herbicides are incompatible with TOPIK because they reduce the effectiveness of TOPIK or because in mixture they may cause crop yellowing.

For treating WILD OATS and broadleaf weeds ONLY

1. No reduction in Wild Oat control occurs when TOPIK is applied as recommended with Tigrex* or Jaguar*. Use 100 mL of a 100% non-ionic surfactant per 100 L of water instead of DC Trate* oil when mixing with Tigrex* or Jaguar*.

2. Some reduction in Wild Oat control may result when TOPIK plus DC Trate* oil is applied with bromoxynil or bromoxynil + MCPA products. Apply mixtures when weeds are actively growing and use TOPIK at the maximum recommended rate.
3. **Incompatible:**
The following herbicides are known to be incompatible with TOPIK:
Ally*, Amber® Post, Diuron, Logran®, MCPA, Barrel* (bromoxynil + dicamba + MCPA). Herbicides which are incompatible with TOPIK must be applied separately. In this situation, apply TOPIK first and then allow at least 10 days between its application and application of the broadleaf weed herbicide.

For treating PARADOXA GRASS and ANNUAL RYEGRASS

Insufficient information is available on the compatibility of TOPIK, used in mixtures with broadleaf weed herbicides, when treating Paradoxa Grass or Annual Ryegrass.

Therefore, in these situations, apply TOPIK first and then allow at least 10 days between its application and application of the broadleaf weed herbicide.

PROTECTION OF CROPS, NATIVE AND OTHER NON-TARGET PLANTS:

OO NOT apply on or near shrubs, trees, lawns or crops other than wheat. DO NOT drain or flush equipment on or near desirable trees or other plants, where their roots may extend, or in situations where by movement of soil or by seepage absorption of the herbicide may occur.

DO NOT apply under meteorological conditions or from spraying equipment which could be expected to cause spray to drift onto nearby susceptible plants, adjacent crops, crop lands or pastures.

OO NOT allow spray to drift onto adjacent fallow land.

PROTECTION OF WILDLIFE, FISH, CRUSTACEA AND ENVIRONMENT:

DO NOT apply to irrigation drains or channels.
DO NOT contaminate dams, streams, creeks and rivers with the chemical, spray mixture, used containers or equipment washings.

STORAGE AND DISPOSAL:

Store in original containers tightly closed in a dry well-ventilated area, away from seeds, fertilisers and other pesticides. DO NOT store for prolonged periods in direct sunlight.

Triple rinse containers with water before disposal, and add rinsings to the tank mix or dispose of rinsate in a disposal pit away from desirable plants and their roots, and watercourses. On-site disposal of unwanted chemicals is unacceptable.

DO NOT re-use containers. Destroy empty containers by breaking, crushing or puncturing them. Dispose of containers at a local authority landfill that does not burn its refuse. If there is no local authority landfill readily available in your area, bury the containers at a depth of 50 cm or more at a licensed/approved disposal site. DO NOT burn empty containers or product.

MATERIAL SAFETY DATA SHEET:

If additional hazard information is required refer to the Material Safety Data Sheet. For a copy phone 1 800 02 5931.

RE-ENTRY PERIOD:

DO NOT enter treated areas without protective clothing until the spray has dried.

SAFETY DIRECTIONS:

Harmful if swallowed. Will irritate the eyes and skin. Repeated exposure may cause allergic disorders. Avoid inhaling spray mist. Avoid contact with eyes and skin.

When opening the container and preparing spray, wear cotton overalls buttoned to the neck and wrist (or equivalent clothing) and a washable hat, elbow-length PVC gloves and face shield or goggles. If product gets on skin, immediately wash area with soap and water. If product gets in eyes, wash it out immediately with water. After use and before eating, drinking or smoking, wash hands, arms and face thoroughly with soap and water. After each day's use, wash gloves, face shield or goggles and contaminated clothing.

FIRST AID:

If poisoning occurs contact a doctor or Poisons information Centre. If swallowed, and if more than 15 minutes from a hospital, induce vomiting, preferably using Ipecac Syrup (APF).

RESISTANCE WARNING:

TOPIK Selective Herbicide is a member of the aryloxy-phenoxypropionate ("fop") group of herbicides. TOPIK has the inhibition of fat (lipid) synthesis mode of action. For weed resistance management TOPIK is a Group A herbicide.

Some naturally-occurring weed biotypes resistant to TOPIK and other inhibition of fat (lipid) synthesis herbicides may exist through normal genetic variability in any weed population. The resistant individuals can eventually dominate the weed population if these herbicides are used repeatedly. These resistant weeds will not be controlled by TOPIK or other fat (lipid) synthesis inhibiting herbicides.

Since the occurrence of resistant weeds is difficult to detect prior to use, Ciba accepts no liability for any losses that may result from the failure of TOPIK to control resistant weeds.

Annual ryegrass biotypes resistant to diclofop-methyl and other "grass specific" herbicides are also often resistant to TOPIK. Before using TOPIK on a population resistant to "grass specific" herbicides, have a resistance test conducted to ensure that it is susceptible to TOPIK.

Large numbers of healthy surviving weeds can be an indication that resistance is developing. Efforts should be made to prevent seed set of the surviving weeds. DO NOT make more than one application of a herbicide with the inhibition of fat (lipid) synthesis mode-of-action to a crop in the same season.

If the user suspects that the target weed population is resistant to herbicides with this mode of action, TOPIK or other fat (lipid) synthesis inhibiting herbicides should not be used.

Strategies to minimise the risk of herbicide resistance are available. Consult your farm chemical supplier, consultant, local Department of Agriculture or Primary Industries, or local Ciba representative for details.

MANUFACTURER'S WARRANTY AND EXCLUSION OF LIABILITY

This product as supplied is of a high grade and believed to be suitable for any purpose for which it is expressly recommended and must be used in accordance with the directions for use given on the label. No responsibility is accepted in respect of this product, save those non-excludable conditions implied by any Federal and State legislation or law of a Territory.

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Topik®

Selective Herbicide

Active Constituents:

300 g/L CLODINAFOP-PROPARGYL

75 g/L CLOQUINTOCET-MEXYL

Complete Directions for Use Inside
- Read before using

L1 433608

ciba

Ciba-Geigy Australia Limited,
140-150 Bungaree Road, Pendle Hill, NSW 2145.

Batch No.	
Date of Manufacture	

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MANUFACTURER'S WARRANTY AND EXCLUSION OF LIABILITY
Product sold subject to manufacturer's warranty and exclusion of liability.

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