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For Agricultural & Veterinary Chemicals

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Public Release Summary

FLUAZURON

in the product

ACATAK
POUR-ON TICK DEVELOPMENT INHIBITOR

This document is published by the
National Registration Authority for
Agricultural and Veterinary Chemicals.

For further information, please contact:

[redacted]

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 Commonwealth Environment Protection Agency (CEPA), 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 "Requirements for Clearance 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. The publication of more technical information to accompany Public Release Summaries is planned for the future.

As a relatively new organisation, the NRA would welcome comment on the usefulness of this document and 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 BE USED 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_o	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

EXECUTIVE SUMMARY

Introduction

The purpose of this document is to provide a summary of the data reviewed and an outline of regulatory considerations for the proposed clearance and registration of the chemical fluazuron for use as a pour-on tick development inhibitor in beef cattle. The information provided herein is a very brief version, presenting only the conclusions reached by the various expert reviewers after consideration of masses of detailed and fully referenced material and trial data. All trial data and methods of assessment presented for evaluation were according to accepted scientific principles and of a standard publishable in reputable refereed journals.

Acatak Pour-on Tick Development Inhibitor, containing the active ingredient fluazuron, is to be used for the treatment of the cattle tick (*Boophilus microplus*).

The National Registration Authority for Agricultural and Veterinary Chemicals (NRA) has completed an assessment of the data submitted by the applicant in support of this use of fluazuron and now invites public comment before deciding whether to proceed to approve this product for use in Australia. The following information is provided for public comment.

Animal Production Aspects

Fluazuron is a new tick development inhibitor. It is a benzoylphenyl urea with highly selective activity against ticks and suitable for systemic use in cattle. It will be marketed as Acatak Pour-on Tick Development Inhibitor.

Beef production is a major primary industry and contributes significantly to Australia's economy. The cattle tick (*Boophilus microplus*) is an important parasite of cattle with a widespread distribution throughout northern Australia costing the industry an estimated $60-100 million annually. Because fluazuron has a novel mode of action, it will provide an additional cattle tick control agent that will not be subject to any resistance induced through previous use of products such as dichlorodiphenyltrichloroethane, organophosphates, synthetic pyrethroids and amidines.

The data package is considered adequate to indicate that Acatak Pour-on Tick Development Inhibitor will control all known resistant strains of cattle tick (*Boophilus microplus*) on beef cattle when used according to the directions on the label.

The safety of fluazuron when administered alone to cattle has been demonstrated in over one thousand cattle in trials. Compatibility of fluazuron with leptospirosis vaccines, anthelmintics, insecticides and vitamin preparations has also been demonstrated.

The major advantage of using Acatak Pour-on Tick Development Inhibitor is that all known resistant strains of cattle tick (*Boophilus microplus*) can be strategically controlled, providing benefits in animal health, production and welfare.

Environmental Aspects

It is likely that fluazuron will be used mainly for free range cattle, however, it could be used in feedlots. Acatak Pour-on Tick Development Inhibitor will be applied to beef cattle using an applicator at a maximum of three treatments annually. The main route of environmental exposure will be from the excrement of treated cattle.

Fluazuron has low potential for toxicity to mammals, birds and plants. By comparison, fluazuron is highly toxic to aquatic invertebrates and moderately toxic to fish. Contamination of watercourses is unlikely, however, since Acatak Pour-on Tick Development Inhibitor demonstrates rain-fastness, is not expected to run off after application, and is unlikely to move either dissolved in run-off or leach through the soil due to its high partition coefficient and low solubility in water.

The main hazard will be to terrestrial invertebrates, in particular those that breed in dung. It is impossible to determine from the available data the effect on dung flora such as dung beetles. While the environmental hazard posed by the proposed use of fluazuron appears to be low, this needs to be verified on the basis of additional data. Consequently, a provisional clearance of two years duration is proposed at this point.

Toxicology

Fluazuron has low acute oral, dermal and inhalation toxicity. It is not a skin or eye irritant, and showed no potential for skin sensitisation. Acatak Pour-on Tick Development Inhibitor which contains 25 g/L fluazuron also has low acute oral and dermal toxicity but it is a severe skin irritant.

Fluazuron has been tested in short- and long-term exposure studies in mice, rats and dogs. In the short-term studies, fluazuron at very high dose rates produced toxic effects mainly on the liver and on blood cells. Long-term studies in rats and dogs did not reveal any major signs of toxicity, but in mice, there were effects on the eyes and reproductive organs at high doses. Fluazuron was not found to be carcinogenic in rats. In mice, the possible relationship between fluazuron and the occurrence of tumours in the intestines and mammary glands was not clear and was considered to be doubtful as an indicator of any significant carcinogenic risk to humans. Fluazuron showed no evidence of a potential to cause birth defects or damage to genetic material (DNA).

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 use of Acatak Pour-on Tick Development Inhibitor.

Residues

Fluazuron residues were detected in cattle treated with Acatak Pour-on Tick Development Inhibitor at the recommended dose rates. The maximum residues were in the fat deposits of the treated animals; in other tissues, the residue levels were much

lower. At the recommended withholding period of 6 weeks, the highest values recorded were 4.4 mg/kg (in the fat), 0.12 mg/kg (in liver) and 0.05 mg/kg (in kidney).

Metabolic studies confirmed fat and then offal were the preferred sites of deposition of residues. No metabolites of fluazuron were detected in the tissues.

Maximum residue limits of 7 mg/kg for cattle meat (in the fat) and 0.5 mg/kg for edible offal of cattle were proposed on the basis of the residue data provided.

Occupational Health and Safety Aspects

Acatak Pour-on Tick Development Inhibitor containing fluazuron presents a minimal safety risk to workers when handled according to instructions on the label and in the Material Safety Data Sheet (MSDS). The risk of developing significant acute and chronic health effects from occupational exposure is low. However, Acatak Pour-on Tick Development Inhibitor may produce eye and skin irritation and skin sensitisation.

To minimise occupational exposure the safety directions on the label must be followed. A copy of the MSDS should be easily accessible to all users/handlers.

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INTRODUCTION

The purpose of this document is to provide the public with a summary of the data reviewed and an outline of regulatory considerations for the proposed use of the chemical fluazuron as a pour-on cattle tick development inhibitor, and to seek public comment prior to the chemical product being approved for use in Australia.

Comments should be sent to:

Applicant

Ciba-Geigy Australia Limited has applied for clearance of a new veterinary drug fluazuron, a tick development inhibitor.

Product Details

Fluazuron will be marketed in the product Acatak Pour-on Tick Development Inhibitor containing fluazuron at 25g/L. Fluazuron interrupts the tick life cycle at different levels by interfering with cuticle formation during development. Because of its novel mode of action, fluazuron will provide an additional cattle tick control agent that will not be subject to any resistance induced through previous use of other products.

Acatak Pour-on Tick Development Inhibitor will be used in areas of Australia where cattle tick (*Boophilus microplus*) is a problem. Accordingly, Queensland, Western Australia and the Northern Territory are the only States/Territory where the product will be cleared for sale and use while in New South Wales the product may be used under Permit.

Overseas Registration Status

No applications for the registration of Acatak Pour-on Tick Development Inhibitor have been lodged overseas at this point.

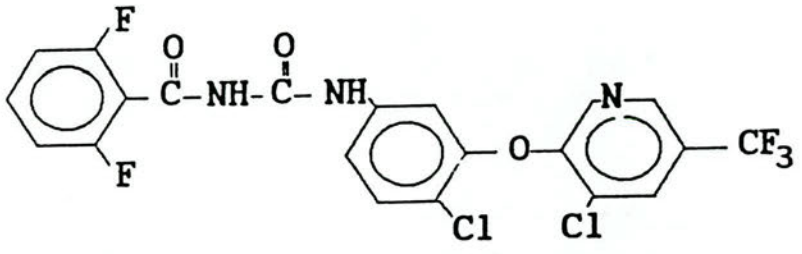
PROPERTIES OF THE CHEMICAL ACTIVE INGREDIENT

Fluazuron is a benzoylphenyl urea compound.

CHEMICAL IDENTITY

Name (IUPAC): chlorophenyl]-	3-[3-(3-chloro-5-trifluoromethyl-2-pyridinyloxy)-4- 1-(2,6-difluorobenzoyl)-urea
Common name:	Fluazuron
Manufacturers code numbers & synonyms:	CGA 157419; FB-785
CAS number:	86811-58-7
Molecular formula:	$C_{20}H_{10}C_{l2}F_5N_3O_3$
Molecular weight:	506.21

Structural formula:



Fluazuron

Purity of active ingredient: Minimum 98%

PHYSICAL-CHEMICAL PROPERTIES

Pure Active Constituent:

Colour:	Clear, light yellowish to amber liquid
Odour:	Slightly ammonical
Specific gravity:	1.031 to 1.061
Viscosity:	15 to 30 mPas
Corrosive hazard:	Non-corrosive
Flash point:	Non-flammable
Dangerous goods classification as per ACTDG:	UN-free

ANIMAL PRODUCTION ASSESSMENT

- **Efficacy**

As part of the global development programme of fluazuron, many trials to determine efficacy against cattle tick *(Boophilus microplus)* have been undertaken in Australia and overseas.

Dose titration studies of Acatak Pour-on Tick Development Inhibitor were conducted in laboratory assays using eight strain variants of the cattle tick. Further titration studies using five major strains of cattle tick were conducted on cattle of varying breeds, ages and under a range of climatic conditions. A dose of 1.5 mg fluazuron/kg bodyweight proved effective against all the strains of cattle tick challenged.

Dose confirmation trials were conducted using the optimal dosage determined in the dose titration trials. These trials were conducted over a wide range of geographic areas in Australia and Brazil. All trials included cattle treated with other registered acaricides which served as positive controls.

Adequate efficacy of Acatak Pour-on Tick Development Inhibitor administered at 1.5 mg fluazuron/kg bodyweight was demonstrated against the major field strains and life cycle stages of the cattle tick.

- **Resistance**

A specific claim for the strategic control of all known resistant strains of cattle tick (*Boophilis microplus*) on beef cattle has been substantiated and approved for Acatak Pour-on Tick Development Inhibitor. This claim covers the following combinations of tick resistance:

dichlorodiphenyltrichloroethane/organophosphate
dichlorodiphenyltrichloroethane/organophosphate/synthetic pyrethroid
organophosphate/synthetic pyrethroid/amidine
organophosphate/synthetic pyrethroid

- **Special conditions**

Acatak Pour-on Tick Development Inhibitor is only for use in strategic treatment programmes for tick control and is not suitable for use in cleaning cattle moving into gazetted cattle tick free areas.

Queensland, Western Australia and Northern Territory are the only States/Territory where this product will be cleared for sale and use. In New South Wales, the product may be used under Permit.

Acatak Pour-on Tick Development Inhibitor is not to be applied to show cattle as a light scurfing may be visible on treated cattle for some time after treatment.

- **Safety to cattle**

The safety of fluazuron to cattle when administered topically (for a systemic mode of action) at the recommended dose rate has been demonstrated in over one thousand cattle being treated in efficacy and safety trials.

Acatak Pour-on Tick Development Inhibitor can be administered concurrently with other common medications used in/on beef cattle in Australia. Compatibility of fluazuron pour-on applied at 1.5 mg/kg bodyweight in conjunction with leptospirosis vaccines, anthelmintics, insecticides and vitamin preparations has been confirmed in field trials. No adverse reactions were observed.

- **Reproductive safety**

No adverse reactions to Acatak Pour-on Tick Development Inhibitor at recommended or elevated dose rates have been observed in pregnant heifers and no effects on cow or bull reproductive performances were observed. Pregnant heifers treated just prior to calving and subsequently following calving had no adverse reactions in the treated heifers nor the untreated calves.

- **Use in/on other species**

Acatak Pour-on Tick Development Inhibitor is not recommended for use in/on animal species other than cattle.

- **Restrictions**

The following conditions apply to the use of Acatak Pour-on Tick Development Inhibitor:

(i) not to be used on lactating cattle producing milk for human consumption,

(ii) calves which have suckled on treated cows must not be slaughtered until they are at least ten months old, and

(iii) users of the product are to wear protective clothing (cotton overalls buttoned to the neck and wrist, washable hat, face shield and wear impervious gloves of natural latex or neoprene) when treating cattle, or handling treated cattle within twenty-four hours of application.

ENVIRONMENTAL ASSESSMENT

Chemistry and Formulation

Fluazuron is an insect growth regulator and is said to be more selective than others in this class. It is to be used to control the cattle tick (*Boophilus microplus*).

Fluazuron has a very low water solubility (≤0.02 ppm), low vapour pressure (1.2×10^{-10} Pa @ 20°C) and a high partition coefficient (log $P_{ow} = 5.1$).

Environmental Exposure

- **Application and use pattern**

Fluazuron will be formulated for use as a pour-on at a concentration of 25 g/L with various solvents and surfactants. It will be used to control cattle ticks in pasture beef cattle, with possible use in feed lots. The pour-on is to be applied at a rate of 1.5 mg/kg using an ACATAK applicator, similar to the standard applicator. It is to be applied at a maximum of 3 treatments per year, at least 12 weeks apart. Acatak Pour-on Tick Development Inhibitor is rain fast and is not expected to run-off after application.

- **Metabolism and excretion by animals**

The main route of environmental exposure will be from the excrement of treated cattle. While no data was presented on the metabolism or the excretion of fluazuron from Acatak Pour-on Tick Development Inhibitor, data from fluazuron injectable was submitted for review.

Studies using the injectable show the compound is only slowly metabolised, the major route of elmination is via the faeces (95%) with less than 3% of that eliminated in the urine. By 16 weeks following injection, 16% of the administered dose was eliminated unchanged and 8% as degradation products.

The peak concentration of fluazuron in the blood, following application as Acatak Pour-on Tick Development Inhibitor, occurred 2-4 weeks after application then slowly declined and corresponded to the concentration in the blood following injection at that time. Using the data from the injectable studies, the peak concentration in the faeces is expected to rise to 100 ppb, 2-4 weeks following application. The concentration then slowly declined to 20 ppb 16 weeks following application of pour-on.

- **Hydrolysis**

The rate of hydrolysis was determined at 95 °C and at environmentally relevant pH, the half lives at 25 °C were estimated to be 896 days, pH 5; 107 days, pH 7 and 64 hours at pH 9.

- **Photodegradation**

Fluazuron showed little photodegradation (2%) after 8 hours exposure to artificial sunlight. Though the test was of very short duration, fluazuron is unlikely to significantly photodegrade.

- **Biodegradation**

A year long degradation study in a single soil was conducted which indicated that fluazuron degraded under aerobic conditions, with the first half life of 26 days and a DT-90 of 218 days. At least 3 degradation products were generated, with one major metabolite (23%) and the others at significantly lower concentrations. After a year, 7% of the applied dose was recovered unchanged. No significant observable negative impact on soil micro-organisms was evident throughout the degradation study.

- **Mobility**

While no test results are available fluazuron is unlikely to move either dissolved in run-off or leach through the soil due to its high partition coefficient (log P_{OW} = 5.1) and low solubility in water ($\leq$ 0.02 ppm at 20°C).

Environmental Effects

- **Avian Toxicity**

Acute oral and subacute dietary studies on quails and ducks indicated acute LD_{50} values of >2000 mg/kg and subacute LD_{50} values of >5200 mg/kg. These results indicate little, if any toxic effects to birds (US EPA rating is practically non-toxic).

- **Aquatic organisms**

The most sensitive fish species (of 4 tested) was the rainbow trout (NOEC 8.3 mg/L, LC_{50} mg/L). The most sensitive aquatic organism was the waterflea, *Daphnia magna (NOEC* 0.041 ug/L, EC_{50} 0.6 ug/L). All tests used a non-toxic solvent to increase solubility and were performed according to internationally accepted guidelines.

- **Non-target Invertebrates**

Fluazuron was screened on a broad range of invertebrates and appears to be a relatively poor insecticide but an effective acaricide. However, there is considerable activity against fleas, lice and sheep blowflies. It is impossible to determine from these results the possible effect on dung flora, in particular dung beetles.

- **Earth worms**

The toxicity of fluazuron against earthworms was determined according to international guidelines and the NOEC and LC_{50} was determined to be >1000 mg/kg.

- **Phytotoxicity**

No studies were performed on the effect of fluazuron on plants, as direct application to plants is unlikely from the pour-on.

There were no adverse effects noted on vegetation during the feld trials/efficacy tests.

Prediction of Environmental Hazard

In Australia there are two methods of raising cattle for beef production, in a feedlot and free range on pasture. It is likely that fluazuron will mainly be used for free range cattle, however, it could be used in feedlots. The other significant use for fluazuron is stud cattle and will be considered part of the free range case below.

- **Fluazuron in cattle excreta in feedlots**

The Queensland Department of Primary Industries (QDPI) have recently prepared a series of farm notes which describe the management of feedlots in Australia, the parameters of which were used for the calculations of environmental hazard.

In general, Australian feedlot operations can be divided into two sections, the distinction being based on the market target. Cattle for domestic consumption are held for 70 - 90 days and have an exit weight between 320 - 375 kg, while those destined for the Japanese market are typically held for 130 - 200 days, with a release weight of 600 kg. Entry weight for both domestic and export markets is ≈ 270 kg.

The concentration of active in the manure released from the feedlot was calculated at 400 ppb. This calculation was based on several assumptions:

- the holding period within the feedlot, 70 days.
- the amount of applied dose ingested by the animal, 25% of applied dose (pour-on folmulations are absorbed by self grooming of the cattle)
- excretion by the animal, estimated at 50% of absorbed dose

The QDPI Feedlot Service model has estimated that the amount of manure produced is directly proportional to the cattle bodyweight (i.e. 6% of bodyweight), thus the amount of active compound released in faeces will be constant irrespective of the weight of the treated animal.

With these factors the concentration in the faeces from the feedlot is 400 ppb. It should be noted that the degradation within the faeces has not been considered.

- **Fluazuron in soil after spreading contaminated manure from feedlot**

Assuming an average plough depth of 15 cm and the spreading of manure as fertiliser at the end of the feedlot holding period (i.e. 70 days), the maximum concentration in soil under Australian conditions was calculated. The worst case concentrations in soil after spreading manure on agricultulal and horticultural land (40 tonnes/ha/year) were calculated at 4.6 and 7.2 ppb respectively. A holding period of 130 days resulted in soil levels of 2.5 and 4.0 ppb.

Pastoral land fertilised with manure from treated cattle would be expected to be walked into the top 1-2 cm of the soil through the grazing of free range cattle and through burying by native and exotic dung beetle species. Therefore the spreading of manure over pastoral land at a rate of 5 tonne/ha could result in 14 ppb fluazuron in the top 1 cm of soil per annum.

Relating the screening toxicity data for the non-target invertebrates studied there is a safety margin of at least an order of magnitude for above ground terrestrial invertebrates (c.f. LC_{50} for sheep blowflies 1 ppm and fleas 0.2 ppm) and 4 orders for earthworms (NOEL 1000 ppm). Toxicities to representative chitin containing soil invertebrate fauna is lacking. However, the high K_{ow} will limit the bioavailability in the soil pore water. Dung beetles are also unlikely to be attracted to the dung/fertiliser as it will be applied in a dry state, worked into the soil and well dispersed through the soil.

- **Fluazuron residue depletion in faeces - outside the feedlot scenario**

In terms of the toxicity of fluazuron towards non-target terrestrial invertebrates, it may be more appropriate to make an assessment based on the concentration of residues in the faeces as determined on a daily basis after treatment.

The notifier has indicated that detectable levels of residues were found in the faeces of cattle for in excess of 16 weeks after treatment. The notifier has not presented any data on the levels of fluazuron in faeces after application of Acatak Pour-on Tick Development Inhibitor, however, the concentration in the faeces from application by injection was presented. From this data, the maximum concentration of fluazuron in the dung pads following application of the pour-on was determined to be 100 ppb, declining to 20 ppb after 16 weeks.

The main hazard will be to terrestrial invertebrates, in particular those that breed in dung. It is impossible to determine from the available results the possible effect on dung flora, in particular dung beetles (which would be the highest exposed and are also commercially valuable). While data are not available for chitin containing invertebrates, the maximum concentration in the dung pads approaches that for the most sensitive screened terrestrial invertebrate (the flea, LC_{50} 220 ppb) and toxicity cannot be ruled out.

The applicant has also done an environmental hazard assessment for cattle in pasture situations. Using the following parameters: three applications per year, 30% is excreted and cattle weight of 400 kg, fluazuron is applied at 540 mg/ha/year to the pasture. Using a higher stocking rate of 7 animals/hectare, the applied rate to the land becomes 3780 mg/ha/year. This will be tramped into the top 1-2 cm of soil giving a concentration of 25 ppb in the top 1 cm of soil. This gives a lower concentration but under less realistic circumstances than above.

- **Hazard to non-target organisms**

- Mammals, birds and plants

There should be no hazard to mammal, birds or plants when fluazuron is used for the control of cattle ticks as directed on the label.

- Soil bacteria/micro-organisms

There was no data on the effect on soil bacteria/micro-organisms. However, as the soil biological activity was not effected during the degradation in soil assay, it is unlikely that there will be toxic effects on soil bacteria/micro-organisms.

- Aquatic organisms

Assuming the active ingredient is directly applied to shallow water (15 cm depth), then the concentration in the water is calculated at 2.5 ppb. This does not take account of periodic rain fall events nor degradation, hydrolysis, strong binding to soil, the low water solubility etc. Fluazuron is highly toxic to aquatic invertebrates, as indicated by the high toxicity to *Daphnia* (EC_{50} 0.6 ppb), but only moderately toxic to fish, with the most sensitive fish being rainbow trout (NOEC 8.3 ppm). There is potential for significant effects on aquatic invertebrates, which is mitigated by the product's high K_{OC}, low water solubility and degradation all of which serve to limit the concentration in receiving waters. Contamination of watercourses is likely to be very low from normal use and limited to very low amounts entering these sorbed to eroded soil particles.

- Terrestrial invertebrates

The submission has no data about the toxicity of fluazuron towards terrestrial invertebrate species. There are no complete studies on terrestrial invertebrates containing chitin apart from bees. The study on bees did not involve the larval stages, where IGR's have maximum effect during moulting/pupating. The screening data shows significant toxicity on two terrestrial invertebrates, fleas and lice. Also, as there is significant toxicity on aquatic invertebrates, fluazuron could have similar toxicity on some terrestrial invertebrates.

Conclusions and Recommendations

Fluazuron is a benzoylphenyl urea growth regulator proposed for use as an acaricide. These compounds inhibit chitin formation and are known to be extremely toxic to juvenile forms of arthropods. Fluazuron is claimed to be more selective than others of this class. However, this is not supported by efficacy screening data and there are a number of deficiencies in the submission. These are:

- the lack of excretion data after pour-on application,
- no data for degradation in dung,
- limited soil degradation data; and
- the lack of toxicity data relevant to chitin containing soil invertebrates such as dung beetles.

As a result a number of assumptions and extrapolations have had to be made in order to clarify the likely environmental hazard posed by the proposed use of fluazuron. While these appear to support a low hazard, this needs to be verified. Consequently at this stage a provisional two year clearance could only be supported pending provision of the above information.

PUBLIC HEALTH AND SAFETY ASSESSMENT

Evaluation of Toxicology

The toxicological database for fluazuron 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 health effects in humans would be expected.

- **Toxicokinetics and Metabolism**

Fluazuron is well absorbed in rats (65%) after oral exposure and extensively metabolised. The tissue distribution showed highest concentrations of fluazuron in the fat followed by the liver and kidney. An elimination half-life of about 13-days was noted in most tissues, with highest residual fluazuron concentrations noted in fat after 12-weeks. Fluazuron and its metabolites are excreted mainly via the faeces.

- **Acute Studies**

Fluazuron had low acute oral, dermal and inhalation toxicity in rats. It is not a skin or eye irritant in rabbits, and showed no potential for skin sensitisation in guinea-pigs.

Acatak Pour-on Tick Development Inhibitor, the formulated product which contains 25 g/L fluazuron, also had low acute oral and dermal toxicity in rats. It is a severe skin irritant in rabbits. While eye irritancy studies have not been conducted, the product has the potential to be a severe eye irritant.

These data confirm the low risk of acute poisoning with Acatak Pour-on Tick Development Inhibitor, but indicate the need to prevent exposure to the skin and eyes.

- **Short-Term Studies**

Short-term gavage or dietary administration of fluazuron in rats for up to 90 days produced slightly increased liver weights (100 mg/kg body weight/day, dietary: 35-60 mg/kg body weight /day, gavage). Other indications of toxicity following dietary administration of fluazuron included enlargement of liver cells, thyroid folicullar cells and pituitary cells. Following dermal administration for 21-days, changes in the clotting time of blood was the only significant adverse effect noted.

In a 4-week dietary study in mice, slight changes to circulating blood cell indices (increased white cells and segmented neutrophils, and decreased lymphocytes) were noted, these effects occurring at the highest dose (1944 mg/kg body weight/day) in females only.

A dietary study for up to 13-weeks in dogs revealed only transitory affects on body weight and food consumption in males at 2067 mg/kg body weight/day.

- **Long-Term Studies**

Long-term dietary administration of fluazuron in mice resulted in lenticular cataracts in the eyes of both sexes at the highest dose (971 mg/kg/day). Lenticular changes consisted of mild necrosis and calcification of the subcapsular lens fibres in the posterior area. In addition, there were slight toxic effects on the uterus in female mice (43 mg/kg body weight/day and above) and the prostate glands in males (971 mg/kg body weight/day only). There was no clear evidence of an increased incidence of tumours related to treatment with fluazuron, although at some sites, (e.g. in the mammary glands and intestines) the tumour incidence appeared to be high in female mice treated with 971 mg/kg body weight/day relative to historical controls. These findings do not suggest a significant cancer risk for humans and were only seen at doses substantially higher than likely levels of human exposure.

In long-term dietary studies in rats (2-years) and dogs (1-year), fluazuron was not significantly toxic at doses up to 782-922 mg/kg body weight /day (rats) or 112-125 mg/kg body weight/day (dogs).

The lowest NOEL was 4 mg/kg body weight/day in the 2-year mouse study and this is consistent with a compound of relatively low toxicity.

- **Reproduction and Developmental Studies**

In a two-generation reproduction study in rats, fluazuron had no effect on reproductive functions or on fertility. Reduced parental body weight gain was noted in the second generation females at 1000 mg/kg body weight/day, and there was a slight reduction in the body weights of the offspring at 75 mg/kg body weight/day.

Fluazuron was administered orally to pregnant rats and rabbits during critical periods of foetal development and there were no birth defects observed in either species.

- **Genotoxicity**

Fluazuron did not induce mutation in *Salmonella* strains or in Chinese Hamster cells. There was no evidence for chromosomal damage in an *in vivo* test in Chinese Hamster bone marrow and in an *in vitro* test with cultured human lymphocytes. Fluazuron also gave negative results in unscheduled DNA synthesis in rat hepatocytes and human fibroblasts.

These data indicate that fluazuron does not damage genetic material (DNA).

Potential For Chemical Residues In Food

Analytical methodology appropriate for the determination of fluazuron in cattle fat and offal was presented and evaluated as being satisfactory. After extraction from the tissue and high performance liquid chromatography, fluazuron residues were determined at 260 nm. The limits of determination of the method were reported as 0.01 and 0.02 mg/kg of fat and offal respectively. Recoveries from the fat were stated to be between 82 and 93 % and from offal 95 to 100%.

Results from six trials on cattle were submitted in support of the application. The trials were conducted in New South Wales and Queensland. Treatment rates used were 2, 3 or 4 mg of fluazuron/kg of body weight of the beast with one to three treatments applied. Multiple treatments were given at intervals of 9 or 12 weeks. The 2 mg/kg of body weight rate represents the highest dose permitted under the label's use pattern. The label also allows a maximum of three treatments per year with at least 12 weeks between treatments recommended. Also submitted in support of the application were five efficacy trials in which some residue data had been generated. In these trials the rates used were either 1.5 or 2.5 mg/kg of body weight with one or two applications. Multiple applications were given at 16 or 24 weeks apart.

In all of the trials, samples for residue analyses were taken at the label's withholding period of 6 weeks; in some cases results from samples taken at periods before and after that time were also reported.

The trial data showed that fat was the site of maximum accumulation of the residue with the levels found in kidney fat and subcutaneous fat being of the same order of magnitude in any individual trial. In animals treated at the maximum label rate and sampled 6 weeks after treatment, residue levels in the fat were generally less than 3 mg/kg; the highest value found was 4.4 mg/kg. The trial in which this value occurred was conducted during a drought period and absence of any substantial increase in the bodyweight of the treated animals was thought to have led to the higher residue levels. As this trial represented a

situation in which maximum residue levels could occur, it was the basis of the setting of the meat (in the fat) MRL at 7 mg/kg.

Residue levels in other tissues were much lower than those found in fat. Following treatment at the maximum rate allowed by the label and with a 6 week withholding period, liver had up to 0.12 mg/kg of fluazuron and kidney up to 0.05 mg/kg. These results lead to the offal MRL being set at 0.5 mg/kg, a value consistent with the data presented.

The metabolism studies presented supported the MRLs proposed and the residue definition of 'fluazuron'. The studies confirmed that the preferred site of deposition was in the fat and then the offal. Fluazuron was the only product found in these sites and the major route of elimination was via the faeces.

Based on the toxicology and potential dietary intake of the residue, it was considered that there should be no adverse effects on human health.

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

TABLE 1

Compound	Food	MRL (mg/kg)
Add:		
Fluazuron		
MO 0812	Cattle, Edible offal of	0.5
MM 0812	Cattle meat [in the fat]	7

and

TABLE 3

Compound	Residue
Add:	
Fluazuron	Fluazuron

PUBLIC HEALTH STANDARDS

The Drugs and Poisons Schedule (Standing) Committee (DPSSC) of the National Health & Medical Research Council considered the toxicity of Acatak Pour-on Tick Development Inhibitor and its active ingredient and assessed the necessary controls to be implemented under States' poisons regulations to prevent the occurrence of poisoning.

The DPSSC recommended that fluazuron 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 product label.

OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

Bcfore end-use

As the fully formulated product will be imported into Australia, potential for exposure exists for workers engaged in transport, storage and retailing. However, the product may be packed in Australia in future. In this case, formulators, storemen and packers will also have potential for exposure. The physicochemical and toxicological properties of fluazuron indicate that it poses low health and safety risks to workers when handled according to instructions. Fluazuron and the end-use product (EUP) are not classified under the Australian Dangerous Goods Code.

End-use

Fluazuron has low acute oral, dermal, and inhalational toxicity and low chronic toxicity. The product has low acute oral and dermal toxicity but is a severe skin irritant. The toxicity of the EUP is influenced by the properties of the non-active ingredients present in the EUP ie 1-methyl-2-pyrrolidinone, 1-octyl-2-pyrrolidinone, and 1-dodecyl-2-pyrrolidinone. Based on the properties of these non-active ingredients, the product is also expected to produce severe eye irritation and skin sensitisation.

End-users will handle the product when treating cattle. The likelihood of significant exposure to the product is reduced due to its presentation in ready-to-use retail packs for use with a special applicator. However, skin would be the main route of exposure. The label requirement to wear overalls, elbow-length gloves and face shield while using the product should reduce the risk to end users of skin and eye irritation and skin sensitisation.

The development of chronic health effects from using this product is unlikely. A worker weighing 70 kg would be needed to absorb approx 12 mL/day of the product based on the No-Observable-Effect- Level (NOEL) in a chronic study in animals. Given the method of use, repeated exposure and absorption of this amount is very unlikely.

Recommendations for the control of worker exposure

Fluazuron is considered to be a non-hazardous substance according to Worksafe Australia classification criteria for workplace substances. The EUP is considered to be a hazardous substance due to its severe skin irritation properties.

Establishment of an occupational exposure standard or health surveillance for fluazuron is not considered necessary by Worksafe Australia at this time.

To minimise occupational exposure to fluazuron the following should be observed:

Information on the label and the MSDS should be consulted prior to using the product. A copy of the MSDS should be easily accessible to all users/handlers of the product.

MSDSs on fluazuron products should meet Worksafe Australia's requirements.

LABELLING

The NRA approved draft label for ACATAK is at Appendix I to this document.

SUGGESTED FURTHER READING

Interim Requirements for Clearance of Agricultural and Veterinary Chemical Products (available from the NRA)

Code of Practice For Labelling Veterinary Chemical Products (available from the NRA)

MRL Standard - Maximum Residue Limits in Food and Animal Feedstuffs (NH&MRC)

APPENDIX I

WARNING
*

NOT TO BE TAKEN
KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS BEFORE OPENING
FOR ANIMAL TREATMENT ONLY

ACATAK®

Pour-on Tick Development Inhibitor

Active Constituent: 25 g/L FLUAZURON

For Strategic Control of the Cattle Tick, *Boophilus microplus,*
(including all known acaricide resistant strains) on Beef Cattle.
In most situations control can be achieved with 1 or 2 treatments a year.

5 LITRES

CIBA-GEIGY Australia Limited, ACN 002 933 717. 140-150 Bungaree Road
Pendle Hill NSW 2145

D10053-N1-5 UN.No. free

* The Poison Schedule of the end-use product may change from S5 to S6 in the foreseeable future. This relates to consideration of solvents contained in the end-use product by the National Drugs and Poisons Scheduling Committee.

Batch Number	
Expiry Date	

Storage
Store below 30°C (Room Temperature). Store in original container tightly closed in a dry, cool place. Store out of direct sunlight.

Disposal of containers and Residual Chemical
Triple rinse containers with detergent and hot water before disposal. Dispose of rinsate in a disposal pit away from desirable plants and their roots and watercourses.

Destroy empty containers by breaking, crushing or puncturing them. Dispose of the 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 an approved disposal site. Do not burn empty containers or product.

Directions for Use

Restraint:

DO NOT treat pregnant cows within 6 weeks of calving to avoid handling stress.

Animals and Pest	States	Bodyweight (kg)	Dose (mL)	No treated per pack	Critical Comments
Beef cattle after weaning Cattle tick *(Boophilus microplus)*	QLD, NT, & WA only	Up to 150 151 to 200 201 to 250 251 to 300 301 to 350 351 to 400 401 to 450 451 to 500 501 to 550 551 to 600 601 to 650 over 650	9 12 15 18 21 24 27 30 33 36 39 3 mL per 50 kg	555 416 333 277 238 208 185 166 151 138 128	1. Retreatments should occur at least 12 weeks after the previous treatment. 2. Maximum number of treatments per year: 3. 3. Follow guidelines for strategic tick control as indicated on this label or specific local guidelines. 4. Apply in two bands, about 7cm wide, on each side of the spine between the rump and the shoulders with ACATAK applicator. Do not use any other applicator. 5. The weight of cattle should be determined by either scales or a weighband. Dose individuals according to the heaviest animal in the mob. Do not underdose. 6. There is no need to treat calves as long as they suckle treated cows. Calves will receive adequate protection from their mother. A reduced length of protection may occur in cows which are suckling calves. 7. ACATAK should not be applied to show cattle as a light scurfiness may be visible for some time after treatment. 8. ACATAK is a Tick Development Inhibitor and kills ticks progressively. It can take 2 to 3 weeks for cattle to be visibly free of ticks. No additional treatment is necessary during that time, even on heavily infested animals. The development inhibiting effect of ACATAK commences within 3 days of treatment. 9. Not suitable for cleaning cattle moving into gazetted cattle tick free areas.

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

WITHHOLDING PERIOD
DO NOT USE LESS THAN 6 WEEKS BEFORE SLAUGHTER FOR HUMAN CONSUMPTION

CALVES WHICH HAVE SUCKLED ON TREATED COWS MUST NOT BE SLAUGHTERED UNTIL THEY ARE AT LEAST 10 MONTHS OLD

NOT TO BE USED ON CATTLE PRODUCING MILK FOR HUMAN CONSUMPTION OR PROCESSING

GENERAL INSTRUCTIONS

ACATAK treated areas - Introduction of new cattle
Tick infested cattle introduced onto properties where an ACATAK treatment regime is in place should be treated with ACATAK *prior* to release.

Handling of Treated Animals
Wear protective clothing recommended under Safety Directions, if handling treated animals within 24 hours of application.

Strategic treatment recommendations

Region	Cattle Breed*	First Treatment	Second Treatment
South East Qld	*Bos taurus* type	Oct to Jan+	3 to 6 months later
	Bos indicus type	Oct to Mar	Not necessary
Central areas of Qld, NT and WA	*Bos taurus* type	Sep to Feb	3 to 6 months later
		Mar to Aug	5 to 6 months later
	Bos indicus type	Oct to Feb	Not necessary
Wet tropical Qld, and coastal areas of NT and WA	*Bos taurus* type	Sept to Mar	4 to 6 months later
		Apr to Aug	5 to 6 months later
	Bos indicus type	Dec to Feb	3 to 4 months later

* *Bos taurus* type: More than 50% British content
Bos indicus type: More than 50% Brahman content

+*Note: During the first year of use the first treatment should be as early as possible in the recommended period. Under particular circumstances an additional ACATAK treatment may be necessary. Contact Ciba Technical Staff for advice on this issue.*

Cleaning instructions
After use wash ACATAK applicator with detergent and hot water. Dispose of the rinsates in a disposal pit away from desirable plants and their roots and watercourses.

SAFETY DIRECTIONS
Harmful if swallowed. Will damage eyes and skin. Avoid contact with eyes and skin. Repeated exposure may cause allergic disorders. When opening the container and using the product wear cotton overalls buttoned to the neck and wrist and a washable hat, elbow length PVC gloves and a face shield. If clothing becomes contaminated with product remove clothing immediately. If product on skin, immediately wash area with soap and water. If product 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 and contaminated clothing.

FIRST AID
If poisoning occurs, contact a doctor or Poisons Information Centre.

Protection of Wildlife, Fish, Crustacea and Environment
Do not contaminate fish ponds, dams, rivers with the product or used containers. The product is very toxic to aquatic invertebrates.

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.

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 is recommended and must be used in accordance with the direction 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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CIBA-GEIGY, Animal Health Division